HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS

RELATED APPLICATIONS

This application is a continuation of U.S. Application Serial No. 10/329,668, filed December 20, 2002, to Martin *et al.*, entitled "HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS," which claims the benefit of priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/342,720, filed December 21, 2001, to Martin *et al.*, entitled "HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS." The disclosures of the above-referenced applications are incorporated by reference herein in their entirety.

FIELD

Compounds, compositions and methods for modulating the activity of nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of orphan nuclear receptors.

BACKGROUND

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev. 15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptor (PPAR)) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-*cis* retinoic

acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression. There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), coding for RXRα, -β, and -γ, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-3020). In the adult liver, RXRα is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol. 20*:4436-4444.

Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for FXR (*infra*).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science 189*:760-763 and O'Malley (1989) *Endocrinology 125*:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

FXR

FXR (originally isolated as RIP14 (retinoid X receptor-interacting protein-14), see, *e.g.*, Seol *et al.* (1995) *Mol. Endocrinol. 9*:72-85) is a member of the nuclear hormone receptor superfamily and is primarily expressed in the liver, kidney and intestine (see, *e.g.*, Seol *et al.*, *supra* and Forman *et al.* (1995) *Cell 81*:687-693). It functions as a heterodimer with the retinoid X receptor (RXR) and binds to response elements in the promoters of target genes to regulate gene transcription. The FXR-RXR heterodimer binds with highest affinity to an inverted repeat-1 (IR-1) response element, in which consensus receptor-binding hexamers are separated by one nucleotide. FXR is part of an interrelated process, in that FXR is activated by bile acids (the end product of cholesterol metabolism) (see, *e.g.*, Makishima *et al.* (1999) *Science 284*:1362-1365, Parks *et al.* (1999) *Science 284*:1365-1368, Wang *et al.* (1999) *Mol. Cell. 3*:543-553), which serve to inhibit cholesterol catabolism. See also, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317.

LXRα and LXRβ

LXRα is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, *e.g.*, Willy, *et al.* (1995) *Gene Dev. 9(9)*:1033-1045). LXRβ, also known as UR (ubiquitous receptor), is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, *e.g.*, Lehmann, *et al.* (1997) *J. Biol. Chem. 272(6)*:3137-3140). LXRα is activated by oxycholesterol and promotes cholesterol metabolism (Peet *et al.* (1998) *Cell 93*:693-704). Thus, LXRs appear to play a role in, *e.g.*, cholesterol metabolism (see, *e.g.*, Janowski, *et al.* (1996) *Nature 383*:728-731).

Nuclear Receptors and Disease

Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, peripheral occlusive

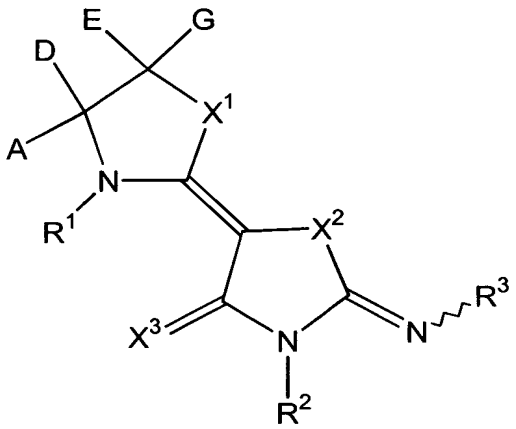
disease, ischemic stroke, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), atherosclerosis and gallstones (see, *e.g.*, International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including FXR, LXRs and/or orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7α-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem. 275*:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317), hyperlipidemia, cholestasis, and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including FXR, LXRs and/or orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

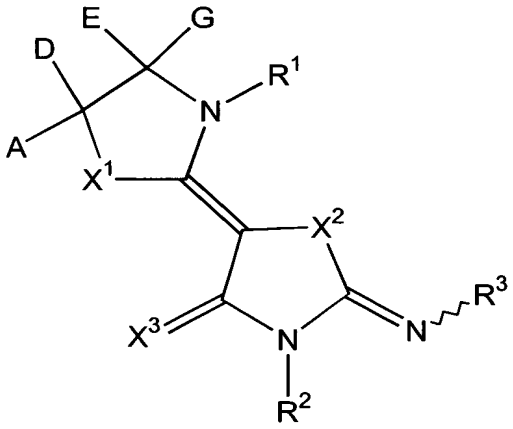
SUMMARY

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR), liver X receptors (LXRα and LXRβ) and/or orphan nuclear receptors, are provided. In certain embodiments, the compounds are heterocyclic compounds that are substituted with a heterocyclylene group and an imine moiety. In one embodiment, the compounds provided herein are agonists of FXR and/or LXR. In another embodiment, the compounds provided herein are antagonists of FXR and/or LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

In one embodiment, the compounds for use in the compositions and methods provided herein have formulae I:



or



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$,

or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

X^1 and X^2 are each independently selected from O, S, S(=O), $S(=O)_2$, Se, NR^5, CR^6R^7 and $CR^8=CR^9$; X^3 is O, S, Se, NR^5 or CR^6R^7; R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; R^3 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; where

R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, $NR^{14}R^{15}$ and $C(=J)R^{13}$;

R^{10}, R^{11} and R^{12} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$;

J is O, S or NR^{14};

R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$;

R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R^1, R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino,

arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene; and

each Q^1 is independently unsubstituted or substituted with one or more substituents, in one embodiment one, two or three substituents, each independently selected from Q^2;

each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy,

perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

each Q^2 is independently unsubstituted or substituted with one or more, in one embodiment one, two or three, substituents each independently selected from alkyl, halo and pseudohalo;

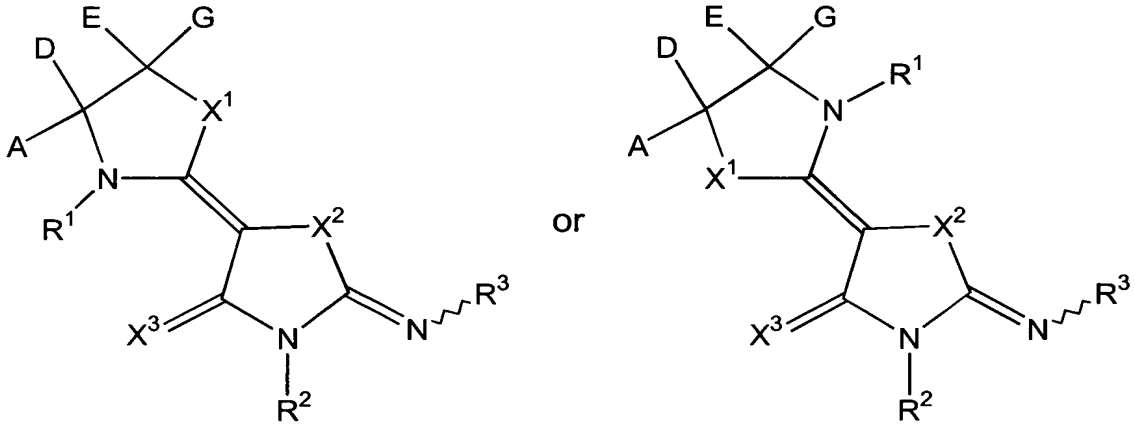
R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae I:



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo,

pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

X^1 and X^2 are each independently selected from O, S, S(=O), $S(=O)_2$, Se, NR^5, CR^6R^7 and $CR^8=CR^9$; X^3 is O, S, Se, NR^5 or CR^6R^7; R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; R^3 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; where

R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, $NR^{14}R^{15}$ and $C(=J)R^{13}$;

R^{10}, R^{11} and R^{12} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$;

J is O, S or NR^{14};

R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$;

R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R^1, R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino,

alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^+R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene; and

each Q^1 is independently unsubstituted or substituted with one or more substituents, in one embodiment one, two or three substituents, each independently selected from Q^2;

each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy,

aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl,

aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$.

In certain embodiments herein, the compounds are selected with the proviso that when R^3 is substituted or unsubstituted heteroarylium then the heteroatom substituent is not alkyl or aryl. In another embodiment, the compounds are selected with the proviso that R^3 is not substituted or unsubstituted heteroarylium or substituted or unsubstituted heteroaryliumalkyl. In other embodiments, the compounds are selected with the proviso that R^3 is not heteroaryl. In further embodiments, the compounds are selected with the proviso that R^3 is not alkyl. In another embodiment, the compounds are selected with the proviso that R^3 is not heterocycloaryl (*i.e.*, an aryl group possessing a fused heterocyclic moiety).

The groups A, D, E, G, X^1, X^2, X^3, R^1, R^2 and R^3 are selected such that the resulting compound has nuclear receptor modulation activity, such as in at least one assay described herein, such as FXR antagonist or agonist activity, and, in certain embodiments, at an IC_{50} or EC_{50} of less than about 100 μM. The FXR IC_{50} or EC_{50} values for the compounds provided herein are, in certain embodiments, less than about 50 μM, 25 μM, 10 μM, 1 μM, 100 nM, 10 nM or 1 nM.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as

but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.

Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular

disorders, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof.

Methods of modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays that measure the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, including the assays provided herein. These methods include inhibiting and up-regulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors.

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided herein are also provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application, for the treatment of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke,

conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are provided.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 provides *in vitro* data for the compounds whose synthesis is described in the Examples. Average EC_{50} ("EC50_AVG") for FXR agonism is provided as follows: A = 0.0001-0.01 μM, B = 0.01-0.1 μM, C = 0.1-1.0 μM, D = 1.0-10.0 μM and NC = not calculated or inactive. Average percent efficacy ("EFF_AVG") for FXR agonism relative to control (chenodeoxycholic acid, CDCA) is provided as follows: A = >150%, B = 100-150%, C = 50-100%, D = 0-50% and NC = not calculated or inactive. Average IC_{50} ("IC50_AVG") for FXR antagonism is provided as follows: A = 0.0001-0.01 μM, B = 0.01-0.1 μM, C = 0.1-1.0 μM and D = 1.0-10.0 μM. Average percent inhibition ("INHIB_AVG") for FXR antagonism relative to control (chenodeoxycholic

acid, CDCA) is provided as follows: E = >75%, F = 50-75%, G = 25-50%, H = 0-25% and NEG = negative.

DETAILED DESCRIPTION OF EMBODIMENTS

A. D finitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors are FXR and LXR.

As used herein, an orphan nuclear receptor is a nuclear receptor for which the natural ligand is unknown.

As used herein, the term farnesoid X receptor or FXR refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative FXR species include, without limitation rat FXR (SEQ ID NO. 5), mouse FXR, and human FXR (SEQ ID NO. 7).

As used herein, liver X receptor or LXR or UR refers to a nuclear receptor implicated in cholesterol homeostasis. As used herein, the term LXR refers to both LXRα and LXRβ, two forms of the protein found in mammals. Liver X receptor-α or LXRα refers to the receptor described in U.S. Patent No.

5,757,661 and Willy *et al.* (1995) *Gene Dev. 9(9)*:1033-1045. Liver X receptor-β or LXRβ refers to the receptor described in Peet *et al.* (1998) *Curr. Opin. Genet. Dev. 8(5)*:571-575; Song *et al.* (1995) *Ann. N.Y. Acad. Sci. 761*:38-49; Alberti *et al.* (2000) *Gene 243(1-2)*:93-103; and references cited therein.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl ar heterocyclyl.

Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl ar heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of FXR activity, in an assay that measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a

drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α-amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the

specific activity of the compound. The instant disclosure is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, *etc.* is used as is generally understood by those of skill in this art.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-penytyl and isohexyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms.

The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," and "substitued cycloalkynyl" refer to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl,

cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above.

As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sulfuryl" refers to $-S(O)_2-$. As used herein, "sulfo" refers to $-S(O)_2O-$.

As used herein, "carboxy" refers to a divalent radical, -C(O)O-.

As used herein, "aminocarbonyl" refers to $-C(O)NH_2$.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to $-C(O)NR'R$ in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula $-NR'COR$ in which R' and R are independently alkyl, including lower alkyl.

As used herein, "diarylaminocarbonyl" refers to -C(O)NRR' in which R and R' are independently selected from aryl, including lower aryl, such as phenyl.

As used herein, "arylalkylaminocarbonyl" refers to -C(O)NRR' in which one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

As used herein, "arylaminocarbonyl" refers to -C(O)NHR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "hydroxycarbonyl" refers to -COOH.

As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, including lower alkyl.

As used herein, "aryloxycarbonyl" refers to -C(O)OR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkoxy" and "alkylthio" refer to RO- and RS-, in which R is alkyl, including lower alkyl.

As used herein, "aryloxy" and "arylthio" refer to RO- and RS-, in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 1 to about 20 carbon atoms, in another embodiment having from 1 to 12 carbons. In a further embodiment alkylene includes lower alkylene. There may be optionally inserted along the alkylene group one or more oxygen, sulfur, including S(=O) and $S(=O)_2$ groups, or substituted or unsubstituted nitrogen atoms, including -NR- and $-N^+RR-$ groups, where the nitrogen substituent(s) is(are) alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or COR', where R' is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -OY or -NYY, where Y is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl. Alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-(CH_2)_3-$), methylenedioxy ($-O-CH_2-O-$) and ethylenedioxy ($-O-(CH_2)_2-O-$). The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. In certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

As used herein, "azaalkylene" refers to -$(CRR)_n$-NR-$(CRR)_m$-, where n and m are each independently an integer from 0 to 4. As used herein, "oxaalkylene" refers to -$(CRR)_n$-O-$(CRR)_m$-, where n and m are each independently an integer from 0 to 4. As used herein, "thiaalkylene" refers to -$(CRR)_n$-S-$(CRR)_m$-, -$(CRR)_n$-S(=O)-$(CRR)_m$-, and -$(CRR)_n$-$S(=O)_2$-$(CRR)_m$-, where n and m are each independently an integer from 0 to 4. In certain embodiments herein, the "R" groups in the definitions of azaalkylene, oxaalkylene and thiaalkylene are each independently selected from hydrogen and Q^1, as defined herein.

As used herein, "alkenylene" refers to a straight, branched or cyclic, in one embodiment straight or branched, divalent aliphatic hydrocarbon group, in certain embodiments having from 2 to about 20 carbon atoms and at least one double bond, in other embodiments 1 to 12 carbons. In further embodiments, alkenylene groups include lower alkenylene. There may be optionally inserted along the alkenylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkenylene groups include, but are not limited to, —CH=CH—CH=CH— and -CH=CH-CH_2-. The term "lower alkenylene" refers to alkenylene groups having 2 to 6 carbons. In certain embodiments, alkenylene groups are lower alkenylene, including alkenylene of 3 to 4 carbon atoms.

As used herein, "alkynylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, in another embodiment 1 to 12 carbons. In a further embodiment, alkynylene includes lower alkynylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkynylene groups include, but are not limited to, —C≡C—C≡C—, -C≡C- and -C≡C-CH_2-. The term "lower alkynylene" refers to alkynylene groups having 2 to 6 carbons. In certain embodiments, alkynylene groups are lower alkynylene, including alkynylene of 3 to 4 carbon atoms.

As used herein, "alk(en)(yn)ylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic

hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, and at least one double bond; in another embodiment 1 to 12 carbons. In further embodiments, alk(en)(yn)ylene includes lower alk(en)(yn)ylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alk(en)(yn)ylene groups include, but are not limited to, —C=C—$(CH_2)_n$-C≡C—, where n is 1 or 2. The term "lower alk(en)(yn)ylene" refers to alk(en)(yn)ylene groups having up to 6 carbons. In certain embodiments, alk(en)(yn)ylene groups have about 4 carbon atoms.

As used herein, "cycloalkylene" refers to a divalent saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments 3 to 6 carbon atoms; cycloalkenylene and cycloalkynylene refer to divalent mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenylene and cycloalkynylene groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenylene groups in certain embodiments containing 4 to 7 carbon atoms and cycloalkynylene groups in certain embodiments containing 8 to 10 carbon atoms. The ring systems of the cycloalkylene, cycloalkenylene and cycloalkynylene groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)ylene" refers to a cycloalkylene group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkylene," "substituted alkenylene," "substituted alkynylene," "substituted cycloalkylene," "substituted cycloalkenylene," and "substitued cycloalkynylene" refer to alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene and cycloalkynylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q^1.

As used herein, "arylene" refers to a monocyclic or polycyclic, in certain embodiments monocyclic, divalent aromatic group, in one embodiment having from 5 to about 20 carbon atoms and at least one aromatic ring, in another

embodiment 5 to 12 carbons. In further embodiments, arylene includes lower arylene. Arylene groups include, but are not limited to, 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons.

As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 members where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "heterocyclylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted arylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three of four substituents, where the substituents are as defined herein, generally selected from Q^1.

As used herein, "alkylidene" refers to a divalent group, such as =CR'R", which is attached to one atom of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, "arylalkylidene" refers to an alkylidene group in which either R' or R" is an aryl group. "Cycloalkylidene" groups are those where R' and R" are linked to form a carbocyclic ring. "Heterocyclylidene" groups are those where at least one of R' and R" contain a heteroatom in the chain, and R' and R" are linked to form a heterocyclic ring.

As used herein, "amido" refers to the divalent group -C(O)NH-. "Thioamido" refers to the divalent group -C(S)NH-. "Oxyamido" refers to the divalent group -OC(O)NH-. "Thiaamido" refers to the divalent group -SC(O)NH-. "Dithiaamido" refers to the divalent group -SC(S)NH-. "Ureido"

refers to the divalent group -HNC(O)NH-. "Thioureido" refers to the divalent group -HNC(S)NH-.

As used herein, "semicarbazide" refers to -NHC(O)NHNH-. "Carbazate" refers to the divalent group -OC(O)NHNH-. "Isothiocarbazate" refers to the divalent group -SC(O)NHNH-. "Thiocarbazate" refers to the divalent group -OC(S)NHNH-. "Sulfonylhydrazide" refers to the group -SO_2NHNH-. "Hydrazide" refers to the divalent group -C(O)NHNH-. "Azo" refers to the divalent group -N=N-. "Hydrazinyl" refers to the divalent group -NH-NH-.

Where the number of any given substituent is not specified (*e.g.*, "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_{1-3}alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the following terms have their accepted meaning in the chemical literature:

AcOH	acetic acid
$CHCl_3$	chloroform
conc	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Hex	hexanes
H_2SO_4	sulfuric acid
MeCN	acetonitrile
MeOH	methanol
Pd/C	palladium on activated carbon
TEA	triethylamine

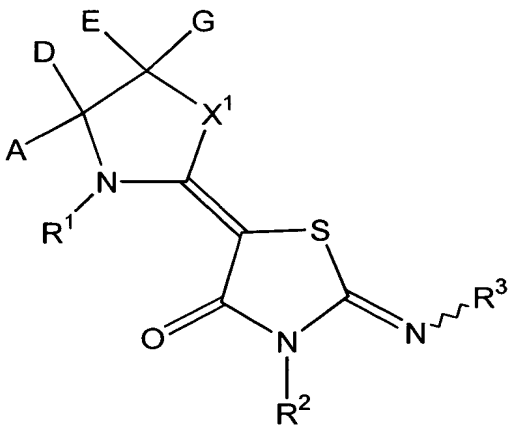
THF	tetrahydrofuran
TFA	trifluoroacetic acid

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

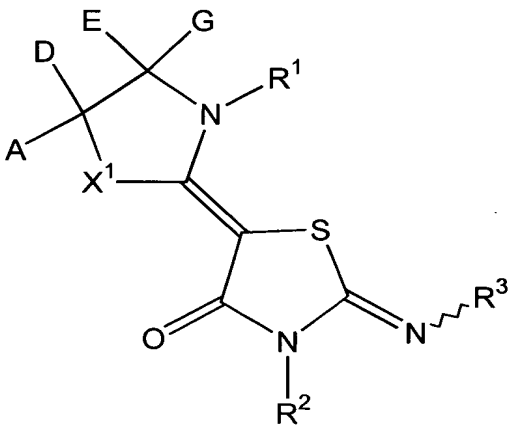
B. Heterocyclic Modulators of Nuclear Receptors

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR), liver X receptors (LXRα and LXRβ) and/or orphan nuclear receptors, are provided.

In certain embodiments, the compounds are thiazolidinones, *i.e.*, compounds of formulae I where X^2 is S and X^3 is O, that are substituted with a heterocyclylene group and an imine moiety. Thus, in these embodiments, the compounds have formulae II:



or



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl,

substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

X^1 is selected from O, S, $S(=O)$, $S(=O)_2$, Se, NR^5, CR^6R^7 and $CR^8=CR^9$; R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; R^3 is hydrogen,

substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; where:

R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, $NR^{14}R^{15}$ and $C(=J)R^{13}$;

R^{10}, R^{11} and R^{12} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$;

J is O, S or NR^{14};

R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$;

R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of R^1, R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino,

haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene;

each Q^1 is independently unsubstituted or substituted with one or more substituents each independently selected from Q^2;

each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy,

aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

each Q2 group is independently unsubstituted or substituted with one or more, in one embodiment one, two or three, substituents each independently selected from alkyl, halo and pseudohalo;

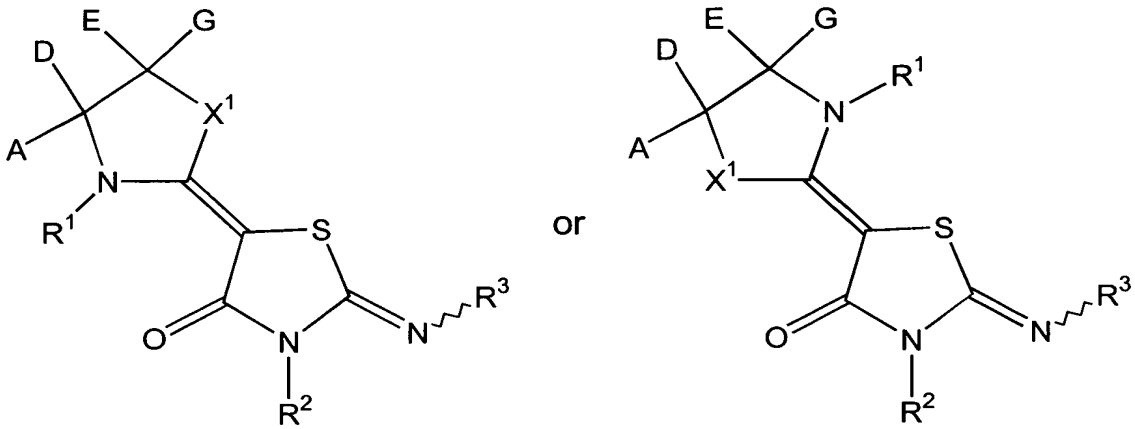
R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$.

In another embodiment, the compounds have formulae II:



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$,

or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

X^1 is selected from O, S, S(=O), $S(=O)_2$, Se, NR^5, CR^6R^7 and $CR^8=CR^9$; R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; R^3 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted

cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ and $C(=J)R^{13}$; where:

R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, $NR^{14}R^{15}$ and $C(=J)R^{13}$;

R^{10}, R^{11} and R^{12} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$;

J is O, S or NR^{14};

R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$;

R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl,

heteroaralkyl and heteroaryliumalkyl moieties of R^1, R^2, R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^+R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$,

dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-$(CH_2)_y$-O-), thioalkylenoxy (*i.e.*, -S-$(CH_2)_y$-O-)or alkylenedithioxy (*i.e.*, -S-$(CH_2)_y$-S-) where y is 1 or 2; or two Q^1 groups, which substitute the same atom, together form alkylene;

each Q^1 is independently unsubstituted or substituted with one or more substituents each independently selected from Q^2;

each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,

N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

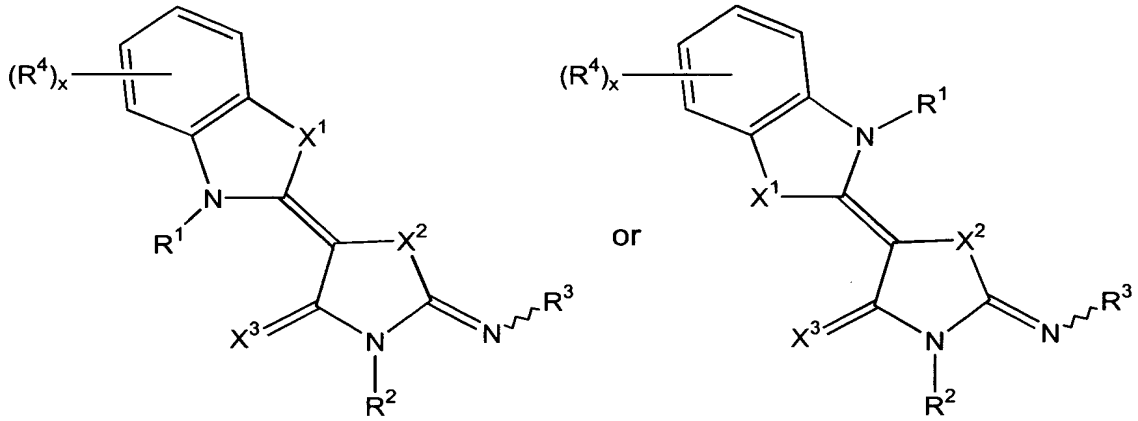
R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$.

In another embodiment, A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, or together form substituted or unsubstituted 1,3-butadienyl. In a further embodiment, A and G are each independently hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted phenyl, or together form 1,3-butadienyl. In another embodiment, A and G are both hydrogen.

In another embodiment, D and E are each hydrogen, or together form a bond.

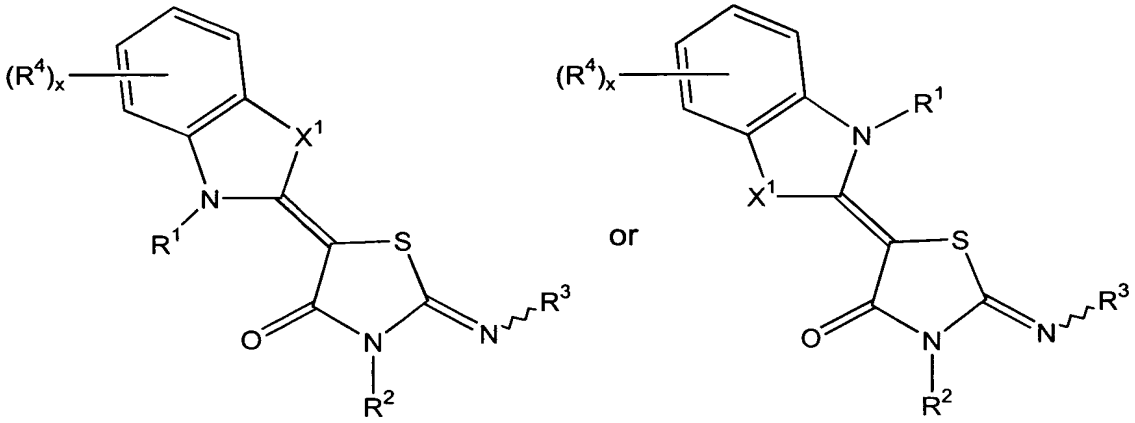
In another embodiment, the compounds for use in the compositions and methods provided herein have formulae I where D and E together form a bond, and A and G together form 1,3-butadienyl. Thus, in this embodiment, the compounds have formulae III:



or a pharmaceutically acceptable derivative thereof, where R^1, R^2, R^3, X^1, X^2 and X^3 are selected as above; each R^4 is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted isothioureido, halo, pseudohalo, OR^{10},

SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ or $C(=J)R^{13}$; x is an integer from 0 to 4; and the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of R^4 are unsubstituted or substituted with one or more substituents each independently selected from Q^2, as defined above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae IV:



or a pharmaceutically acceptable derivative thereof, where R^1, R^2, R^3, X^1, X^2 and X^3 are selected as above; each R^4 is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted isothioureido, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{11}R^{12}$ or $C(=J)R^{13}$; x is an integer from 0 to 4; and the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of R^4 are unsubstituted or substituted with one or more, in certain embodiments one to three or four, substituents each independently selected from Q^2, as defined above.

In certain embodiments herein, the compounds are of formulae III or IV, and are selected with the proviso that when R^3 is substituted or unsubstituted heteroarylium then the heteroatom substituent is not alkyl or

aryl. In another embodiment, the compounds are of formulae III or IV, and are selected with the proviso that R^3 is not substituted or unsubstituted heteroarylium or substituted or unsubstituted heteroaryliumalkyl. In other embodiments, the compounds are of formula III or IV and are selected with the proviso that R^3 is not heteroaryl. In further embodiments, the compounds are of formula III or IV and are selected with the proviso that R^3 is not alkyl. In another embodiment, the compounds are of formula III or IV and are selected with the proviso that R^3 is not heterocycloaryl (*i.e.*, an aryl groups possessing a fused heterocyclic moiety).

In certain embodiments herein, X^1 is O, S or NR^5. In other embodiments, X^1 is O or S. In another embodiment, X^1 is S.

In other embodiments, R^1 is substituted or unsubstituted alkyl. In further embodiments, R^1 is methyl.

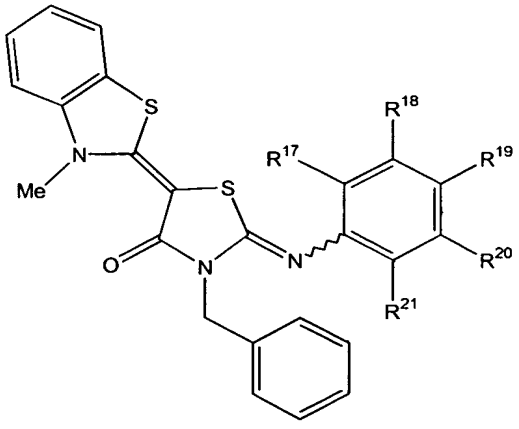
In another embodiment, R^2 is substituted or unsubstituted alkyl or substituted or unsubstituted aralkyl. In further embodiments, R^2 is ethyl, n-butyl or benzyl. In another embodiment, R^2 is benzyl. In another embodiment, R^2 is substituted or unsubstituted heteroaralkyl. In another embodiment, R^2 is pyridylmethyl. In another embodiment, R^2 is picolyl (*i.e.*, 2-, 3-, or 4-pyridylmethyl). In another embodiment, R^2 is 2-furylmethyl. In another embodiment, R^2 is 3-pyridylmethyl.

In another embodiment, R^3 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In further embodiments, R^3 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl, or substituted or unsubstituted quinolinyl. In another embodiment, R^3 is substituted or unsubstituted quinolyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted isoquinolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted indazolyl. In certain embodiments, R^3 is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl. In another embodiment, R^3 is substituted or unsubstituted phenyl.

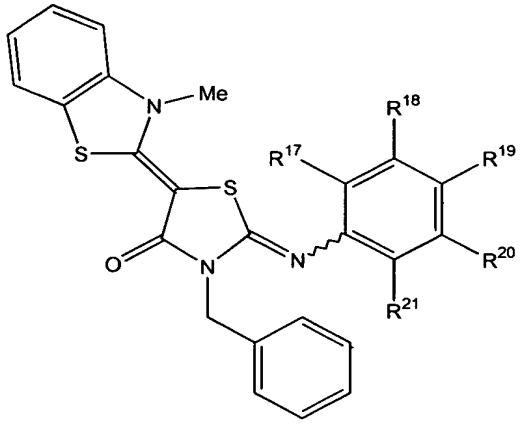
In another embodiment, Q^1 is selected from halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl,

alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino, dialkylcarbonyloxy or heterocyclyl; or two Q^1 groups, which substitute atoms in a 1,2 arrangement, form alkylenedioxy. In another embodiment, Q^1 is selected from halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino, dialkylcarbonyloxy or heterocyclyl; or two Q^1 groups, which substitute atoms in a 1,2 arrangement, form alkylenedioxy. In further embodiments, Q^1 is methoxy, dimethylamino, NH_2, benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl, acetyl, chloro, n-propyl, ethoxy, methylcarbonylamino, $CONH_2$, methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, dimethylaminocarbonyloxy, 2-hydroxyethoxy, 2-(N-morpholinyl)ethoxy or morpholinyl, or two Q^1 groups, which substitute atoms in a 1,2 arrangement, form methylenedioxy. In another embodiment, Q^1 is hydroxycarbonyl or ethylamino.

In further embodiments, the compounds for use in the compositions and methods provided herein are of formulae IV where x is 0, R^1 is methyl, R^2 is benzyl, X^1 is S and R^3 is a substituted or unsubstituted phenyl group. Thus, in these embodiments, the compounds have formulae V:



or



or a pharmaceutically acceptable derivative thereof, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from hydrogen, halo, pseudohalo,

hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy,

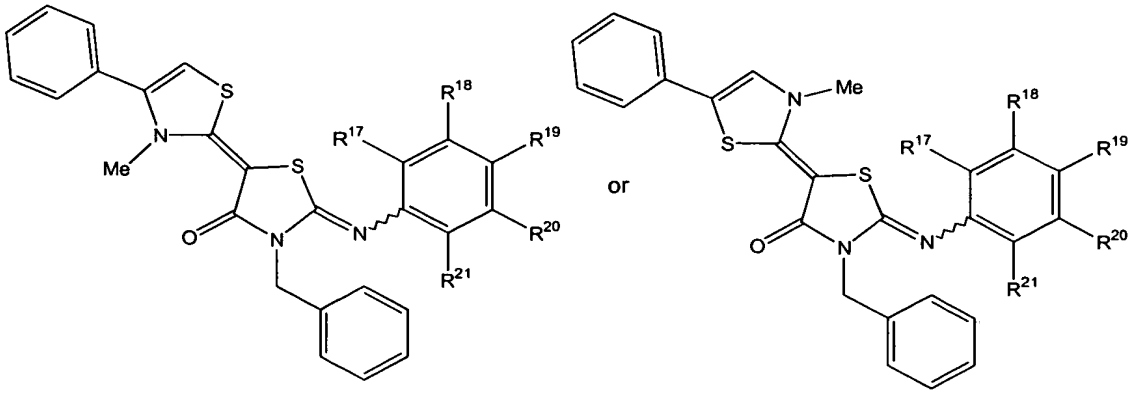
diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which substitute adjacent carbons on the ring, together form alkylenedioxy; and

the aryl and heteroaryl groups of R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from R^{30}, where R^{30} is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.

In another embodiment, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from hydrogen, halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino or heterocyclyl; or any two of R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which substitute adjacent carbons on the ring, form alkylenedioxy. In further embodiments, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently hydrogen, methoxy, dimethylamino, NH_2, benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl, acetyl, chloro, n-propyl, ethoxy, methylcarbonylamino, $CONH_2$, methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-butylamino, 2,2,2-trifluoroethylamino, piperidinyl or morpholinyl, or any two of R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which substitute adjacent carbons on the ring, form methylenedioxy.

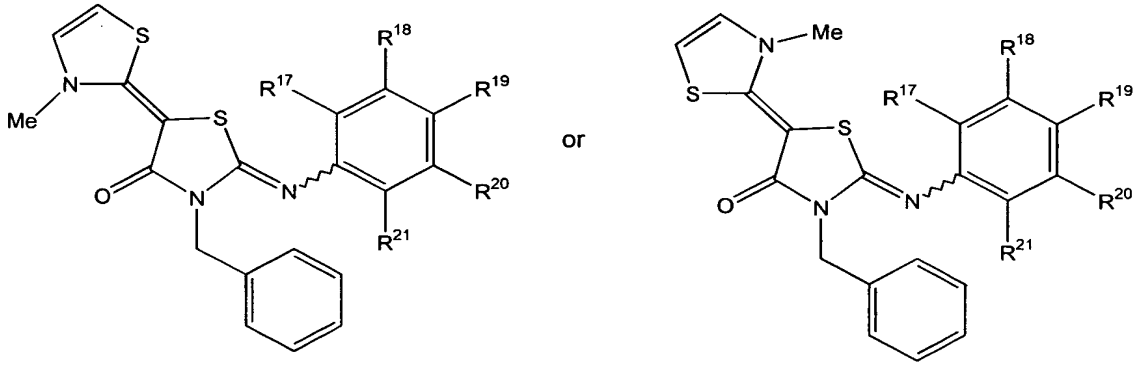
In another embodiment, A is phenyl which is unsubstituted or is substituted with one or more, in one embodiment, one, two or three, groups each independently selected from Q^1.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X^1 is S; R^1 is methyl; R^2 is benzyl; A is phenyl; G is hydrogen; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae VI:



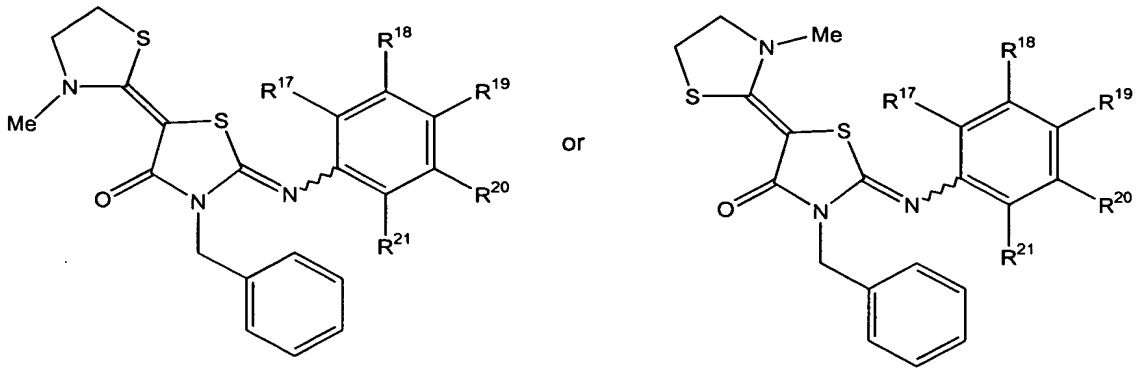
or a pharmaceutically acceptable derivative thereof, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X^1 is S; R^1 is methyl; R^2 is benzyl; A and G are hydrogen; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae VII:



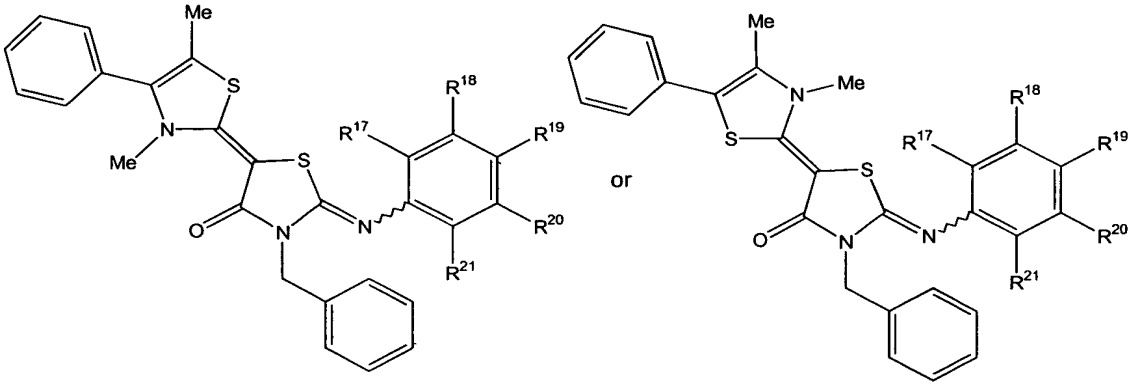
or a pharmaceutically acceptable derivative thereof, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X^1 is S; R^1 is methyl; R^2 is benzyl; and A, G, D and E are hydrogen. Thus, in this embodiment, the compounds have formulae VIII:



or a pharmaceutically acceptable derivative thereof, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X^1 is S; R^1 is methyl; R^2 is benzyl; A is phenyl; G is methyl; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae IX:



or a pharmaceutically acceptable derivative thereof, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are selected as above.

In another embodiment, the compounds provided herein have formulae V-XI, where R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from (i) or (ii) as follows:

(i) R^{21} is ethylamino; R^{18} is cyano; and R^{17}, R^{19} and R^{20} are each hydrogen; or

(ii) R^{17} is ethylamino; R^{20} is cyano; and R^{18}, R^{19} and R^{21} are each hydrogen.

In certain embodiments, the compounds have formulae I, where X^1, X^2 and X^3 are selected from (i) or (ii) as follows: (i) X^1, X^2 and X^3 are each independently S, O or NR^5; or (ii) X^1 is $-CR^8=CR^9-$, where R^8 and R^9 are as

defined herein, and X^2 and X^3 are each independently S, O or NR^5; R^1 is substituted or unsubstituted alkyl, where there are 0 to 6 substituents selected from alkoxy, alkoxyalkyl, hydroxycarbonyl, alkylcarbonyloxy, hydroxy, halo, pseudohalo, aryl and heteroaryl; R^2 is substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaralkyl, or substituted or unsubstituted heterocyclylalkyl; where there are 0 or 1 substituents selected from alkoxycarbonyl and hydroxycarbonyl; R^3 is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; where there are 0 to 5 substituents selected from alkylamino, cyano, cycloalkyl, hydroxy, alkoxy, dialkylamino, amino, heterocyclyl, aralkoxy, alkyl, nitro, haloalkyl, alkylcarbonyl, halo, alkylcarbonylamino, alkoxyalkylcarbonyl-amino, dialkylaminoalkylcarbonylamino, aminocarbonyl, alkoxycarbonyl, aralkylamino, cycloalkylamino, heterocyclylamino, haloalkylamino, haloalkoxy, hydroxycarbonyl, aminosulfonyl, alkylcarbonylaminosulfonyl, or haloalkylcarbonylamino, or any two substituents, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy; A and G are each independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, hydroxycarbonyl, and substituted or unsubstituted alkylcarbonyl, where there are 0 to 5 substituents selected from aryl, haloalkyl, haloalkoxy, nitro, halo, pseudohalo, hydroxy, alkyl and alkoxy, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene or substituted or unsubstituted 1,3-butadienylene, in one embodiment substituted or unsubstituted alkylene, where there are 0 to 4 substituents selected from halo, pseudohalo, alkoxy, nitro, haloalkyl, alkylcarbonylamino, hydroxy, alkylaminocarbonyloxy, alkoxycarbonylalkoxy, aminocarbonylalkoxy, hydroxyalkoxy, alkyl, haloalkylaminocarbonyloxy and alkylaminoalkoxy; D and E are each hydrogen, or together form a bond; and R^5 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted

cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{14}R^{15}$ or $C(=J)R^{13}$; R^{10} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$; J is O, S or NR^{14}; R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$; R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of R^5, R^{10} and R^{13} are unsubstituted or substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl,

arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or

alkylenedithioxy; or two Q^1 groups, which substitute the same atom, together form alkylene; each Q^1 is independently unsubstituted or substituted with one or more substituents each independently selected from Q^2; each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^+R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$,

dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-$(CH_2)_y$-O-), thioalkylenoxy (*i.e.*, -S-$(CH_2)_y$-O-)or alkylenedithioxy (*i.e.*, -S-$(CH_2)_y$-S-) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -$NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -$NR^{70}R^{71}$.

In certain embodiments, the compounds have formulae I, where X^1, X^2 and X^3 are each independently S, O or NR^5; R^1 is substituted or unsubstituted alkyl, where there are 0 to 6 substituents selected from halo, pseudohalo, aryl and heteroaryl; R^2 is substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaralkyl, or substituted or unsubstituted heterocyclylalkyl; where there are 0 or 1 substituents selected from alkoxycarbonyl and hydroxycarbonyl; R^3 is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; where there are 0 to

5 substituents selected from alkylamino, cyano, cycloalkyl, hydroxy, alkoxy, dialkylamino, amino, heterocyclyl, aralkoxy, alkyl, nitro, haloalkyl, alkylcarbonyl, halo, alkylcarbonylamino, aminocarbonyl, alkoxycarbonyl, aralkylamino, cycloalkylamino, heterocyclylamino, haloalkylamino, haloalkoxy, hydroxycarbonyl, aminosulfonyl, alkylcarbonylaminosulfonyl, or haloalkylcarbonylamino, or any two substituents, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy; A and G are each independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl and substituted or unsubstituted alkylcarbonyl, where there are 0 to 5 substituents selected from nitro, halo, pseudohalo, alkyl and alkoxy, or A and G together form substituted or unsubstituted alkylene or substituted or unsubstituted 1,3-butadienylene, in one embodiment substituted or unsubstituted alkylene, where there are 0 to 4 substituents selected from halo, pseudohalo, alkoxy, nitro, haloalkyl, alkylcarbonylamino, hydroxy, alkylaminocarbonyloxy, alkoxycarbonylalkoxy, aminocarbonylalkoxy, hydroxyalkoxy, alkyl, haloalkylaminocarbonyloxy and alkylaminoalkoxy; D and E are each hydrogen, or together form a bond; and R^5 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR^{10}, SR^{10}, $S(=O)R^{13}$, $S(=O)_2R^{13}$, $NR^{14}R^{15}$ or $C(=J)R^{13}$; R^{10} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or $C(=J)R^{13}$; J is O, S or NR^{14}; R^{13} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR^{16} and $NR^{14}R^{15}$; R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of R^5, R^{10} and R^{13} are unsubstituted or substituted with one or more substituents each independently selected from Q^1, where Q^1 is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl,

alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^+R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^1 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two Q^1 groups, which substitute the same atom, together form alkylene; each Q^1 is independently unsubstituted or substituted with one or more substituents each independently selected from Q^2; each Q^2 is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy,

perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido, $-N^{+}R^{51}R^{52}R^{53}$, $P(R^{50})_2$, $P(=O)(R^{50})_2$, $OP(=O)(R^{50})2$, $-NR^{60}C(=O)R^{63}$, dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q^2 groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, $-O-(CH_2)_y-O-$), thioalkylenoxy (*i.e.*, $-S-(CH_2)_y-O-$)or alkylenedithioxy (*i.e.*, $-S-(CH_2)_y-S-$) where y is 1 or 2; or two Q^2 groups, which substitute the same atom, together form alkylene;

R^{50} is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$, where R^{70} and R^{71} are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R^{70} and R^{71} together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R^{51}, R^{52} and R^{53} are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{60} is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R^{63} is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or $-NR^{70}R^{71}$.

In certain embodiments, the compounds claimed herein exhibit improved *in vitro* activity, efficacy, potency and/or pharmacokinetic properties, such as solubility, oral half-life, bioavailability, oral absorption, and/or *in vivo* activity, over related commercially available compounds or related compounds disclosed previously.

In certain embodiments, A and G are selected with the proviso that A and G are not both methyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted at the 5-position with methoxy or chloro and is not substituted at the 6-position with methoxy or methyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted at the 5-position with alkoxy or halo and is not substituted at the 6-position with alkoxy or alkyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted with methoxy, methyl or chloro. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted with alkoxy, alkyl or halo.

In another embodiment, X^1 is S. In another embodiment, X^1 is $-CR^8=CR^9-$. In another embodiment, X^2 is S. In another embodiment, X^3 is O.

In another embodiment, R^1 is substituted alkyl. In another embodiment, R^1 is 2-methoxy-1-ethyl, 3-methoxy-1-propyl, methoxycarbonylmethyl, hydroxycarbonylmethyl, 2-acetoxy-1-ethyl or 2-hydroxy-1-ethyl. In another embodiment, R^1 is unsubstituted alkyl. In other embodiments, R^1 is methyl.

In another embodiment, R^2 is benzyl, phenyl, allyl, ethyl, butyl, cyclohexyl, propyl, 3-pyridylmethyl, 2-furylmethyl, 4-methoxycarbonylbenzyl, 4-hydroxycarbonylbenzyl, 2-phenethyl or 2-(4-morpholinyl)ethyl. In another embodiment, R^2 is benzyl. In another embodiment, R^2 is pyridylmethyl. In another embodiment, R^2 is picolyl (*i.e.*, 2-, 3-, or 4-pyridylmethyl). In another embodiment, R^2 is 2-furylmethyl. In another embodiment, R^2 is 3-pyridylmethyl.

In another embodiment, R^3 is substituted or unsubstituted quinolyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted isoquinolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted indazolyl. In another embodiment, R^3 is substituted or unsubstituted phenyl. In other embodiments, R^3 is substituted with 0 to 5 substituents selected from ethylamino, cyano, cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl, methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, methoxymethylcarbonylamino, dimethylaminomethylcarbonylamino, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl, aminosulfonyl, methylcarbonylaminosulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy. In further embodiments, R^3 is 5-quinolyl, 2-ethylamino-5-cyanophenyl, 4-cyclohexylphenyl, 2-hydroxy-1-naphthyl, 6-quinolyl, 3-methoxyphenyl, 4-dimethylaminophenyl, 4-aminophenyl, 4-(4-morpholinyl)phenyl, 2-methylamino-5-cyanophenyl, 2-dimethylamino-5-cyanophenyl, 2-ethylaminophenyl, 3-cyanophenyl, 2-aminophenyl, 2-isopropylamino-5-cyanophenyl, 4-benzyloxyphenyl, 2-methyl-4-hydroxy-5-isopropylphenyl, 2-ethylamino-5-nitrophenyl, 3-trifluoromethylphenyl, 3-methylcarbonylphenyl, 3-chlorophenyl, 2-propylphenyl, 2-ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-aminocarbonylphenyl, 3-methoxycarbonylphenyl, 8-quinolyl, 8-hydroxy-5-quinolyl, 2-butylamino-5-cyanophenyl, 2-benzylamino-5-cyanophenyl, 2-cyclopentylamino-5-cyanophenyl, 2-(1-pyrrolidinyl)amino-5-cyanophenyl, 5-

isoquinolyl, 1-isoquinolyl, 4-methylcarbonylaminophenyl, 2-t-butylamino-5-cyanophenyl, 2-(2,2,2-trifluoroethyl)amino-5-cyanophenyl, 2-piperidinyl-5-cyanophenyl, 4-methylcarbonylphenyl, 4-aminocarbonylphenyl, 2-ethylamino-5-methoxymethylcarbonylaminophenyl, 2-ethylamino-5-dimethylaminomethyl-carbonylaminophenyl, 1-naphthyl, 2-naphthyl, 2-pyridyl, 3-pyridyl, 2-ethoxy-5-methylcarbonylaminophenyl, 4-pyridyl, 4-methoxycarbonylphenyl, 4-trifluoromethoxyphenyl, 5-indazolyl, 4-(imidazol-1-yl)phenyl, 3,4-methylenedioxyphenyl, 3-hydroxycarbonylphenyl, 2-ethylamino-5-methylcarbonylphenyl, 4-aminosulfonylphenyl, 4-methylcarbonylaminosulfonylphenyl, 3-methylcarbonylphenyl, 2-methylcarbonylamino-5-pyridyl, 4-cyano-3-methylcarbonylaminophenyl, 2-methylamino-5-methylcarbonylphenyl, 4-trifluoromethylcarbonylaminophenyl, 2-ethylamino-5-methoxycarbonylphenyl, 2-hydroxycarbonylphenyl or 2-ethylamino-5-t-butoxycarbonylphenyl.

In another embodiment, A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted methyl, substituted or unsubstituted naphthyl, hydroxycarbonyl, substituted and unsubstituted ethoxycarbonyl, and substituted or unsubstituted methylcarbonyl, or A and G together from substituted or unsubstituted butylene, substituted or unsubstituted propylene, substituted or unsubstituted methyleneazaethylene, or substituted or unsubstituted 1,3-butadienylene. In other embodiments, A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted methyl, substituted or unsubstituted naphthyl, and substituted or unsubstituted methylcarbonyl, and are substituted with 0 to 4 substituents selected from chloro, bromo, methoxy, fluoro, ethoxy, nitro, trifluoromethylcarbonylamino, dimethylaminocarbonyloxy, 2-(1-piperidinyl)ethoxy, 2-(1-methyl-4-piperazinyl)ethoxy, 2-(N-morpholinyl)ethoxy, 2-dimethylaminoethoxy, hydroxycarbonylmethoxy, methylcarbonylamino, phenyl, trifluoromethyl, trifluoromethoxy, hydroxy, ethylaminocarbonyloxy, methoxycarbonylmethoxy, aminocarbonylmethoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, methyl, 2-chloroethylaminocarbonyloxy and 2-methylaminoethoxy. In further embodiments, A and G together form substituted or unsubstituted 1,3-

butadienylene and are substituted with 0 to 5 substituents selected from nitro, fluoro, chloro, methyl and methoxy. In another embodiment, A and G are each independently selected from hydrogen, 4-phenylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylphrnyl, 4-trifluoromethoxyphenyl, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, methyl, 2-naphthyl, 4-bromophenyl, 2-methoxyphenyl, 3-fluorophenyl, 2,4-dimethoxyphenyl, ethoxycarbonyl, benzyl, hydroxycarbonyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, phenyl and methylcarbonyl, or A and G together form 1,3-butadienylene, 2-chloro-1,3-butadienylene, 2-methoxy-1,3-butadienylene, 2-fluoro-1,3-butadienylene, 2-ethoxy-1,3-butadienylene, 2-nitro-1,3-butadienylene, 2-trifluoromethyl-1,3-butadienylene, 2-trifluoromethoxy-1,3-butadienylene, 2-methylcarbonylamino-1,3-butadienylene, 2-trifluoromethylcarbonylamino-1,3-butadienylene, 2-aminocarbonylmethoxy-1,3-butadienylene, 2-(2-hydroxyethoxy)-1,3-butadienylene, 2-(3-hydroxypropoxy)-1,3-butadienylene, 2-dimethylaminocarbonyloxy-1,3-butadienylene, 2-(1-piperidinyl)ethoxy-1,3-butadienylene, 2-(4-(1-methylpiperazin)yl)ethoxy-1,3-butadienylene, 2-(4-morpholinyl)ethoxy-1,3-butadienylene, 2-dimethylaminoethoxy-1,3-butadienylene, 2-hydroxycarbonylmethoxy-1,3-butadienylene, 2-hydroxy-1,3-butadienylene, 2-ethylaminocarbonyloxy-1,3-butadienylene, 2-methoxycarbonylmethoxy-1,3-butadienylene, 2-aminocarbonylmethoxy-1,3-butadienylene, 2-(2-hydroxyethoxy)-1,3-butadienylene, 1-methoxy-1,3-butadienylene, 1-methyl-1,3-butadienylene, 1-chloro-1,3-butadienylene, 2-(2-chloroethylaminocarbonyloxy)-1,3-butadienylene or 2-(2-methylaminoethoxy)-1,3-butadienylene.

In another embodiment, D and E are each hydrogen or together form a bond.

In certain embodiments herein, the compounds are selected from the following compounds. In other embodiments, the compounds are selected from those disclosed in the Examples. All isomers of these compounds are within the scope of the disclosure herein:

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-phenylimino-thiazolidine-4-one;

3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidine-4-one;

2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;

3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one;

2-(3-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-propyl-phenylimino)thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidine-4-one;

3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-thiazolidine-4-one;

N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethoxyphenyl}acetamide;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one;

4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoro-methoxy)phenylimino]thiazolidine-4-one;

3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-thiazolidin-4-one;

3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;

3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;

3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile;
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(*tert*-butylamino)benzonitrile;
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile;
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile;
2-[5-acetyl-2-(ethylamino)phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidin-4-one;
3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-yl-phenylimino)thiazolidin-4-one;
3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;
4-dimethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;
3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidin-4-one;
N-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)phenyl]acetamide;
2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;
3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;

N-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)phenyl]acetamide;

N-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylidene-amino)phenyl]acetamide;

3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;

4-ethylamino-3-[3-benzyl-5-(3-methyl-5-chloro-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyclohexylphenyl)imino-thiazolidine-4-one;

3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-thiazolidine-4-one;

4-ethylamino-3-[3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

4-ethylamino-3-[3-benzyl-5-(3-methyl-5-methoxy-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-quinolyl)imino-thiazolidine-4-one;

4-ethylamino-3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-benzylimino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-quinolyl)imino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-hydroxy-5-quinolyl)imino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-isoquinolyl)imino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-isoquinolyl)imino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonylamino)phenylimino-thiazolidine-4-one;

3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonyl)phenylimino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-aminocarbonyl)phenylimino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-naphthyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-naphthyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-pyridyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-aminosulfonyl)phenylimino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonylaminosulfonyl)phenylimino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-methylcarbonyl)phenylimino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylcarbonylamino-5-pyridyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyano-5-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-trifluoromethyl-carbonylaminophenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methoxycarbonylphenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxycarbonylphenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-tert-butoxycarbonylphenyl)imino-thiazolidine-4-one;

4-butylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-cyclopentylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-pyrrolidinylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-pyrrolidinyl-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-hydroxy-2-methyl-5-isopropylphenyl)imino-thiazolidine-4-one;
3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-thiazolidine-4-one;
4-ethylamino-3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(6-nitro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(6-methylcarbonylamino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-ethylaminocarbonyloxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

4-ethylamino-3-[3-benzyl-5-(5-methoxycarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-aminocarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(4-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(4-methyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(4-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-(2-chloroethylaminocarbonyloxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(5-(2-methylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-propyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-acetylphenyl)imino-thiazolidine-4-one;
3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-(2-furylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
3-(4-methoxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
3-(4-hydroxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
4-ethylamino-3-[3-(2-phenylethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

4-ethylamino-3-[3-(2-(4-morpholinyl)-1-ethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
3-benzyl-5-(3-methylthiazolin-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
3-benzyl-5-(3-methylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-dimethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenyl-5-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-ethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-nitrophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-fluorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-chlorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methylphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methoxyphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methyl-5-acetylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-propylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-diphenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile; and
3-(4-methoxycarbonylbenzyl)-5-(3-methyl-4,5-butylenyllthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one.

In certain embodiments herein, the compounds provided herein are FXR or LXR antagonists. In these embodiments, the compounds have formulae I, where A and G are each independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted methyl, substituted or unsubstituted ethyl or together form substituted or unsubstituted butadienylene where there are 0 to 4 substituents, in one embodiment 0 or 1 substituents, selected from methylcarbonylamino, hydroxy, trifluoromethoxy, trifluorocarbonylamino, aminocarbonylmethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, dimethylaminocarbonyloxy, 2-(1-piperidinyl)ethoxy, 2-(4-(1-methylpiperazin)yl)ethoxy, 2-(4-morpholinyl)ethoxy, 2-dimethylaminoethoxy and hydroxycarbonylmethoxy; D and E form a bond; X^1 and X^2 are both S; X^3 is O; R^1 is methyl; R^2 is benzyl; and R^3 is 5-cyano-2-ethylaminophenyl.

In certain embodiments, FXR or LXR antagonists provided herein are selected from the following compounds. All isomer of these compounds are within the scope of the disclosure herein:
3-(3'-Benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;
3-(3'-Benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;
3-(3'-Benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;

3-[3'-Benzyl-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
3-[3'-Benzyl-4-(2-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
3-[3'-Benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
3-[3'-Benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
N-{2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxo-thiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-acetamide;
3-[3-Benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]-4-ethylamino-benzonitrile;
3-[3-Benzyl-5-(3-methyl-6-trifluoromethoxy-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]-4-ethylamino-benzonitrile;
N-{2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxo-thiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-2,2,2-trifluoroacetamide;
2-{2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}-acetamide;
3-{3-Benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;
3-{3-Benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;
Dimethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
3-{3-Benzyl-5-[3-methyl-5-(2-piperidin-1-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;
3-(3-Benzyl-5-{3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3H-benzothiazol-2-ylidene}-4-oxothiazolidin-2-ylideneamino)-4-ethylamino-benzonitrile;
3-{3-Benzyl-5-[3-methyl-5-(2-morpholin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;
3-{3-Benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile; and

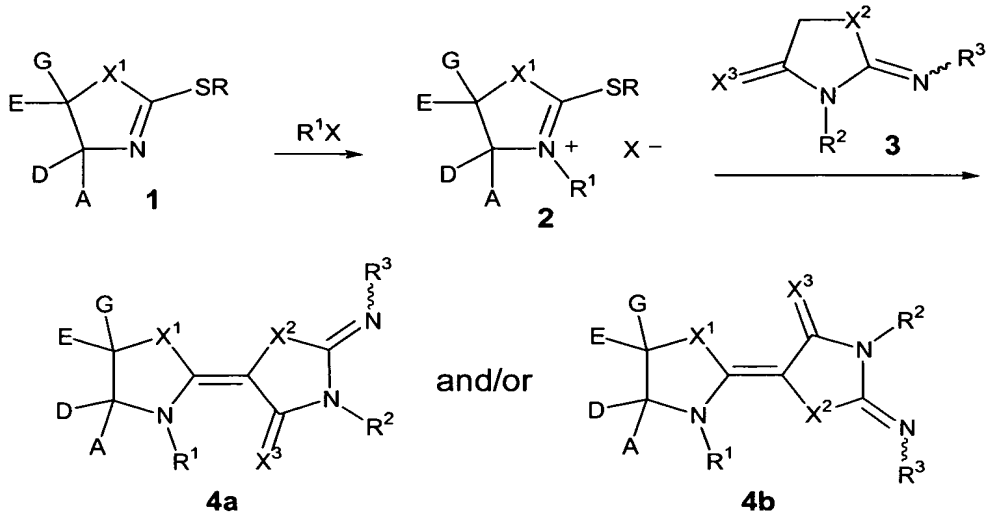
{2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}-acetic acid.

In another embodiment, the compounds for use in the compositions and methods provided herein are shown in the Examples. All isomers of these compounds are within the scope of this disclosure.

C. Preparation of the compounds

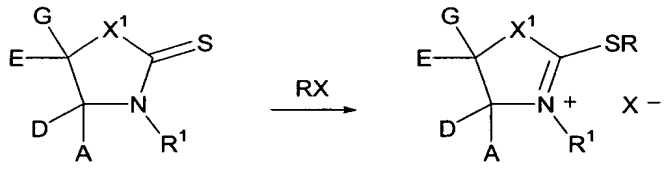
Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low-resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem. 43*, 2923).

The following illustrations depict general preparations of compounds claimed herein and consist of reactions typically known to one skilled in the art of chemical synthesis. The substituents A, D, E, G, R^1-R^3 and X^1-X^3 have been previously described. Also it will be apparent to one skilled in the art that many of the products could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers.

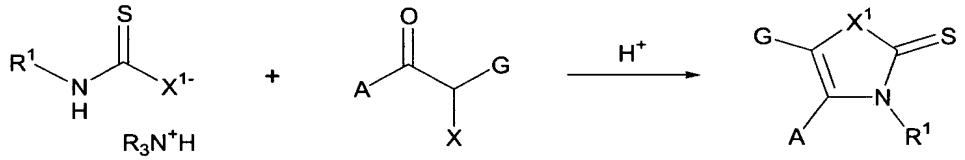


As shown above, treatment of 2-(alkylthio)azole (**1**) with an alkylating agent (R^1X) affords the corresponding 2-(alkylthio)azolium complex (**2**), which then is condensed with 2-iminoazolidine (**3**) in the presence of a base to yield heterocycle (**4**). Thus, for example, when **1** is a 1,3-heterocycle such as thiazole (X^1 = S; E and D form a bond) that is alkylated with methyl *p*-toluenesulfonate, an intermediate *N*-methyl thiazolium complex **2** is prepared (see, *e.g.*, U.S. Patent Nos. 5,707,794 and 2,388,963). Subsequently, for example, when **3** is an 2-iminothiazolidinone (X^2 = S and X^3 = O), an 2-imino-5-(thiazol-2-ylidene)thiazolidin-4-one **4** is generated. Likewise, other heterocycles **1**, such as but not limited to thiazoles, thiazolines, benzimidazoles, benzoxazoles, quinolines, pyridines and indoles, should undergo this transformation when bearing a 2-alkylthio or 2-mercapto substituent.

The synthesis of intermediate **2** is alternatively prepared from the corresponding thione precursor (**5**) upon alkylation with RX. For example, when **5** is thiazolin-2-thione (X^1 = S) that is alkylated with methyl *p*-toluenesulfonate (RX), an intermediate *N*-alkyl 2-(thiomethyl)thiazolinium complex **2** is generated.

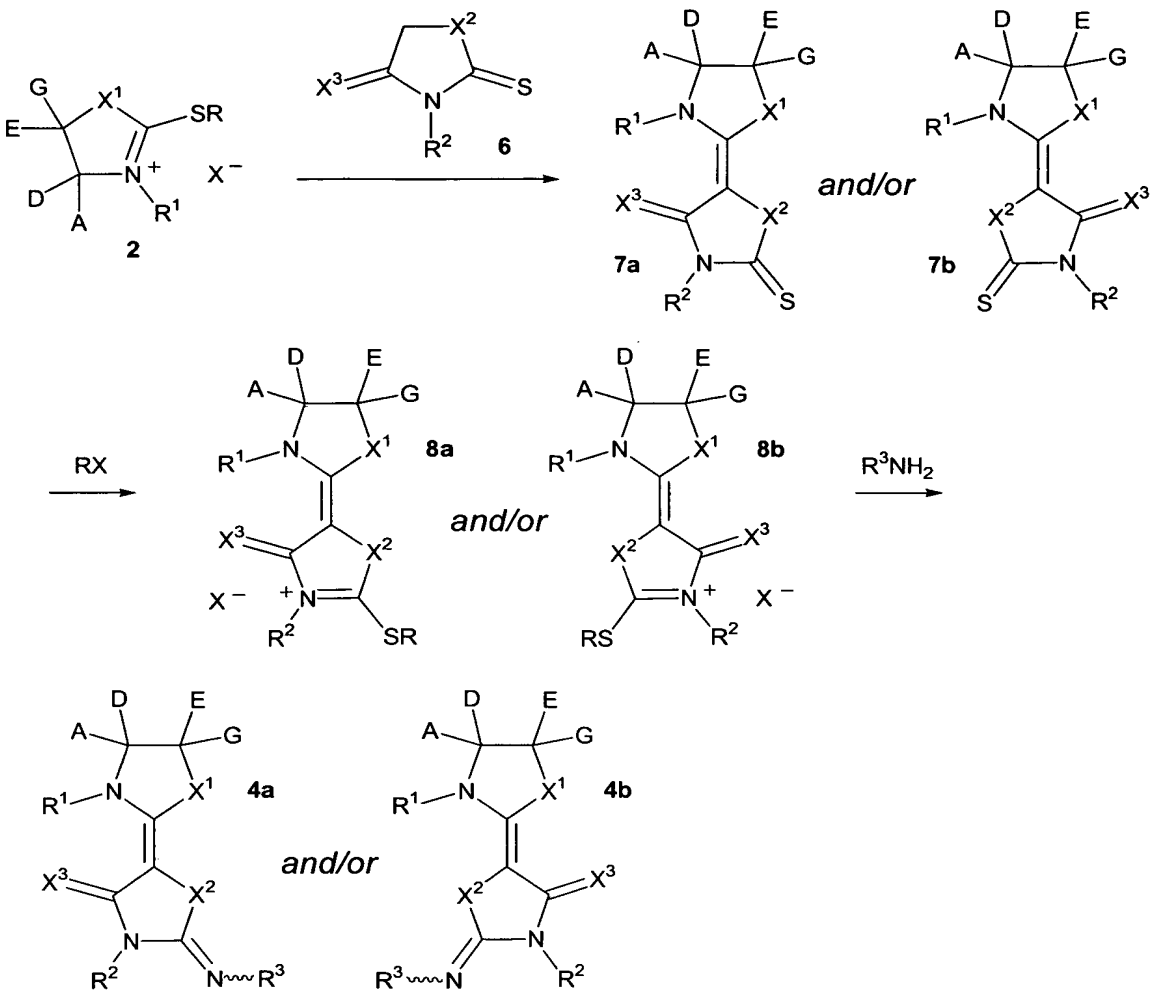


Furthermore, for example, when the thione precursor **5** is thiazole-2-thione (X^1 = S; E and D form a bond), it can be prepared by the condensation of a dithiocarbamate salt (X^1 = S) with a α-haloketone, as depicted below (see, *e.g.*, Bellec *et al.* (1999) *Chem. Mater. 11*:3147; Humphlett *et al.* (1964) *J. Org. Chem. 29*:2146). Various dithiocarbamate salts are synthesized, for example, by reacting a primary amine, *e.g.*, methylamine, with carbon disulfide in the presence of a base such as Et_3N (see, *e.g.*, Humphlett *et al.* (1964) *J. Org. Chem. 29*:2146). The thiazole-2-thione **5** can then be transformed into the corresponding thiazolium complex **2**.

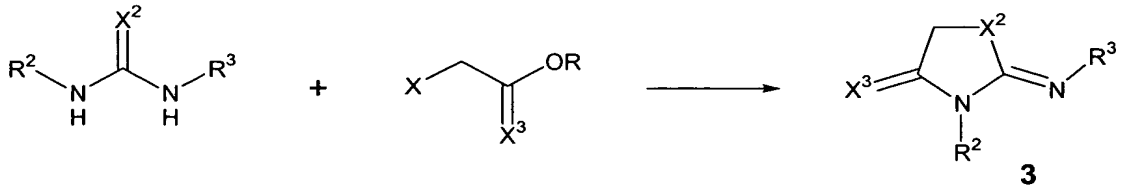


5

Alternatively, as depicted below, reaction of intermediate **2** with azolidin-2-thione (**6**) in the presence of base gives another azolidin-2-thione (**7**). Treatment of intermediate **7** with an alkylating agent (RX) affords the 2-(alkylthio)azolium complex (**8**), which reacts with an amine in the presence of base to yield heterocycle **4**. Thus, for example, when **6** is a 1,3-heterocycle such as rhodanine (X^2 = S and X^3 = O) that is condensed with an intermediate *N*-methyl benzothiazolium complex **2** (X^1 = S; E and D form a bond; A and G form a fused benzene), a 5-(benzothiazol-2-ylidene)thiazolidin-4-one-2-thione **7** is generated (see, *e.g.*, U.S. Patent Nos. 5,618,831 and 2,454,629). Subsequently intermediate **7** is alkylated with, for example, methyl *p*-toluenesulfonate to give a 5-(benzothiazol-2-ylidene)-2-methylthio-4-oxothiazolidinium complex **8**, which can react with, for example, an aniline to yield an 2-imino-5-(benzothiazol-2-ylidene)thiazolidin-4-one **4** (see, *e.g.*, U.S. Patent No. 5,618,831).

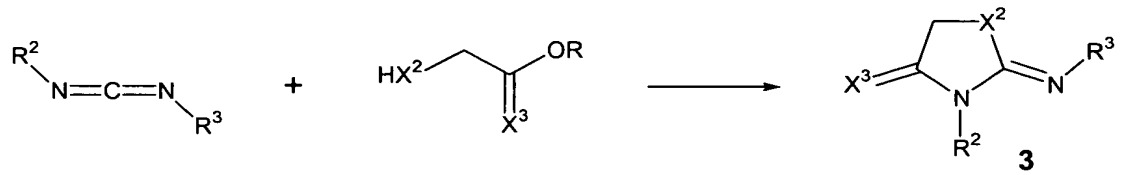


In general, 2-iminoazolidines **3** may be prepared as depicted below. Thus, for example, when **3** is an 2-imino-4-thiazolidinone (X^2 = S and X^3 = O), it can be prepared by condensing a thiourea (X^2 = S) with a 2-haloester (X^3 = O) in the presence of base, in which R^3 is typically aryl or heteroaryl (see, *e.g.*, Seada *et al.* (1993) *Indian J. Heterocycl. Chem.* 3:81; and International Patent Application Publication No. WO 00/42031).



Likewise 2-iminoazolidines **3** may be prepared from a carbodiimide as depicted below. For example, when **3** is an 2-imino-4-imidazolidinone (X^2 = NR and X^3 = O), it can be prepared by reacting a carbodiimide with a 2-

aminoester (X^2 = NR and X^3 = O). Also an 2-imino-4-oxazolidinones (X^2 and X^3 = O) can be prepared from a carbodiimide and a 2-hydroxyester.



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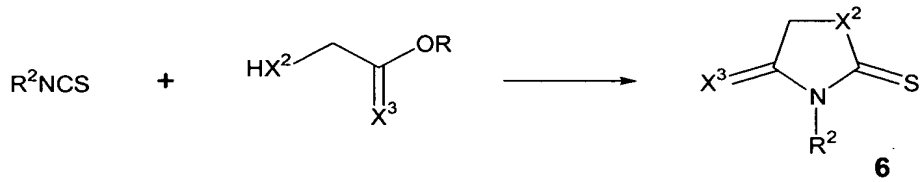
Similarly azolidine-2-thiones **6** may be prepared as depicted below. Thus, for example, when **6** is a rhodanine (X^2 = S and X^3 = O), it can be prepared by condensing an isothiocyanate with a 2-mercaptoester (see, *e.g.*, Dogan *et al.* (1992) *Tetrahedron 48*:7157; and Drobnica *et al.* (1972) *Chem. Zvesti 26*:538). Also imidazolidin-4-one-2-thiones (X^2 = NR and X^3 = O) or oxazolidin-4-one-2-thiones (X^2 and X^3 = O) can be prepared by reacting an isothiocyanate with 2-aminoester or 2-hydroxyester, respectively.



6

Alkyl and aryl isothiocyanates, aryl amines, rhodanines, unsymmetrical carbodiimides and thioureas may be synthesized utilizing known methodology (see, *e.g.*, Katritzky *et al.* (1984) *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, UK; Katritzky *et al.* (2000) *Handbook of Heterocyclic Chemistry,* 2nd Ed.; Pergamon Press: Oxford, UK; March *Advanced Organic Chemistry*, 4th Ed.; John Wiley: New York (1992); and International Patent Application Publication No. WO 00/42031). For example, alkyl and aryl isothiocyanates are readily prepared from reaction of an amine with thiophosgene or a thiophosgene equivalent, *e.g.* thiocarbonyl diimidazole. Many isothiocyanates also are commercially available. Unsymmetrical thioureas are prepared from reaction of an isothiocyanate with an amine.

D. Formulation of pharmaceutical compositions

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

The compositions contain one or more compounds provided herein. The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* **1985**, 126).

In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents,

or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in International Patent Application Publication Nos. 99/27365 and 00/25134 (see, *e.g.*, EXAMPLES 53 and 54) and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 µg/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person

administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as

sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a

single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium

saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

1. Compositions for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar

nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other

enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and

may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a

pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

2. Injectables, solutions and emulsions

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein.

Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral

administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is

sufficient for ameliorating the symptoms of the condition and may be empirically determined.

3. Lyophilized powders

Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

4. Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams,

aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

5. Compositions for other routes of administration

Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa

butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

6. Articles of manufacture

The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material

suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

E. Evaluation of the Activity of the Compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including the FXR. Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, *J. Biomolecular Screening*, 7 No. 1 3-10 (2002)), as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays (see, Lehmann. *et al., J. Biol Chem.,* 272(6) 3137-3140 (1997).

High throughput screening systems are commercially available *(see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., Biomol Screen 2000 Oct;5(5):297) scintillation proximity

assays (SPA) (see for example, Carpenter et *al.*, Methods Mol Biol 2002;190:31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, J Steroid Biochem Mol Biol 2002 Jul;81(3):217-25; (Zhou *et al.*, Mol Endocrinol. 1998 Oct;12(10):1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of FXR with RXRα can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to FXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear

receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXRα is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds of the present invention. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor (See for example US Patents Nos. 5,071,773; 5,298,429 and 6,416,957).Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene, which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as FXR, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include rat FXR (SEQ ID NO. 5), human FXR (SEQ ID NO.7), human RXR α (SEQ ID NO. 9), human RXR β (SEQ ID NO. 17), human RXR γ (SEQ ID NO. 15), human LXR α (SEQ ID NO. 1), human LXR β (SEQ ID NO. 3),human PPARα (SEQ ID NO. 11) and human PPAR δ (SEQ ID NO. 13).

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence) which is linked in turn to the various response elements.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) Gene 66 1-10; Kain, S.R. (1997) Methods. Mol. Biol. 63 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., *et al.*, (1989) J. Chemilum. Biolum. 4 99-111), chloramphenicol acetyltransferase (See Gorman *et al.*, Mol Cell Biol. (1982) 2 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) Annu. Rev. Biochem. 67 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of

the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / Umud super families are used.

A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the

reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of FXR may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by FXR and other nuclear receptors in *vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by FXR target genes. Genes that are known to be regulated by the FXR include cholesterol 7 a-hydroxylase (CYP7A1), the rate limiting enzyme in the conversion of cholesterol to bile acids, the small heterodimer partner-1 (SHP-1), the bile salt export pump (BSEP, ABCB11), canalicular bile acid export protein, sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) and intestinal bile acid binding protein (I-BABP).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDR^{-/-}$) and atherosclerosis using both the Apo $E(^{-/-})$ and $LDL(^{-/-})$ mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally FXR or LXR animal models

(e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (*see*, for example, Sinal, *et al., Cell*, 102: 731-744 (2000), Peet, *et al., Cell,* 93:693-704 (1998)).

F. Methods of use of th compounds and compositions

Methods of use of the compounds and compositions provided herein are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.

Methods of reducing cholesterol levels and of modulating cholesterol metabolism are provided. As described above, FXR is implicated in modulating cholesterol metabolism, catabolism and absorption of dietary cholesterol. See, *e.g.*, International Patent Application Publication No. 00/40965.

Method of altering nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, by contacting the receptor with one or more compounds or compositions provided herein, are provided.

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels are provided.

Methods of treatment, prevention, or amelioration of one or more symptoms of hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915); hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818); hypertriglyceridemia, lipodystrophy, hyperglycemia or diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917); dyslipidemia, obesity, atherosclerosis, lipid disorders, cardiovascular disorders, or gallstone disease (see, *e.g.*, International Patent Application Publication No. WO 00/37077); acne vulgaris or acneiform skin conditions (see, *e.g.*, International Patent Application Publication No. WO 00/49992); atherosclerosis, diabetes,

Parkinson's disease, inflammation, immunological disorders, obesity, cancer or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334); conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, or conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444) are provided.

Methods of increasing cholesterol efflux from mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of increasing the expression of ATP-Binding Cassette (ABC1) in mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Further provided herein are methods for the treatment, prevention, or amelioration of one or more symptoms of cholestasis, as well as treating the complications of cholestasis by administering a compound provided herein.

Cholestasis is typically caused by factors within the liver (intrahepatic) or outside the liver (extrahepatic) and leads to the accumulation of bile salts, bile pigment bilirubin, and lipids in the blood stream instead of being eliminated normally.

Intrahepatic cholestasis is characterized by widespread blockage of small ducts or by disorders, such as hepatitis, that impair the body's ability to eliminate bile. Intrahepatic cholestasis may also be caused by alcoholic liver disease, primary biliary cirrhosis, cancer that has spread (metastasized) from another part of the body, primary sclerosing cholangitis, gallstones, biliary colic and acute cholecystitis. It can also occur as a complication of surgery, serious injury, infection, or intravenous feeding or be drug induced. Cholestasis may also occur as a complication of pregnancy and often develops during the second and third trimesters.

Extrahepatic cholestasis is most often caused by choledocholithiasis (Bile Duct Stones), benign biliary strictures (non-cancerous narrowing of the

common duct), cholangiocarcinoma (ductal carcinoma) and pancreatic carcinoma. Extrahepatic cholestasis can occur as a side effect of many medications.

Accordingly, compounds provided herein may be used for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis, including without limitation, biliary artesia, obstetric cholestasis, neonatal cholestasis, drug induced cholestasis, cholestasis arising from Hepatitis C infection, chronic cholestatic liver disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Methods of treating, preventing, or ameliorating one or more symptoms of hypocholesterolemia using the compounds and compositions provided herein are also provided.

G. Combination Therapy

Also contemplated herein is combination therapy using a compound provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives. The compound provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a FXR selective compound and one or more additional active agents, as well as administration of the FXR selective compound and each active agent in its own separate pharmaceutical dosage formulation. For example, a FXR agonist or antagonist of the present invention and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds described herein and one or more additional active agents can be administered at essentially the same time, *i.e.,* concurrently, or at separately staggered times, *i.e.,* sequentially; combination therapy is understood to include all these regimens.

The compound is preferably administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see,* U.S. Patent No. 4,231,938); simvastatin (ZOCOR®; *see,* U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see,* U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see,* U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see,* U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see*, U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the methods of the present invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry,* pp. 85-89 (5

February 1996). In presently preferred embodiments, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and, more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

The compounds of the present invention can be utilized in methods for decreasing hyperglycemia and insulin resistance or for methods of treating type II diabetes. The compounds can be identified, formulated, and administered as described above.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, *e.g.*, LeRoith, D. *et al.*, (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes Association, diabetes mellitus is

estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDEM); and type 2 diabetes (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk

factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, see, e.g., Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. Ann. Chim. Med. (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (see, e.g., Garcia, M. J. et al., Diabetes (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997) 5(4): 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., et al., Arteriosclerosis (1978) 30: 153-162).

The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (see, e.g., Reaven, G. M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and Flier, J. Ann Rev. Med. (1983) 34:145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose

production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, has been referred to as "Syndrome X" (see, e.g., Reaven, G. M., Physiol. Rev. (1995) 75: 473-486).

The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood glucose, referred to as "hyperglycemia." Type 2 diabetes often occurs in the face of normal, or even elevated, levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that insulin secretion can not compensate for the resistance of peripheral tissues to respond to insulin. In addition, many type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of type 1 or type 2 diabetes.

The term "complication" of diabetes includes, but is not limited to, microvascular complications and macrovascular complications. Microvascular complications are those complications which generally result in small blood vessel damage. These complications include, e.g., retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys). Macrovascular complications are those complications which generally result from

large blood vessel damage. These complications include, e.g., cardiovascular disease and peripheral vascular disease. Cardiovascular disease refers to diseases of blood vessels of the heart. See. e.g., Kaplan, R. M., et al., "Cardiovascular diseases" in HEALTH AND HUMAN BEHAVIOR, pp. 206-242 (McGraw-Hill, New York 1993). Cardiovascular disease is generally one of several forms, including, e.g., hypertension (also referred to as high blood pressure), coronary heart disease, stroke, and rheumatic heart disease. Peripheral vascular disease refers to diseases of any of the blood vessels outside of the heart. It is often a narrowing of the blood vessels that carry blood to leg and arm muscles.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated cholesterol level; (2) hypertriglyceridemia, i.e., an elevated triglyceride level; and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.

The term "cholesterol" refers to a steroid alcohol that is an essential component of cell membranes and myelin sheaths and, as used herein, incorporates its common usage. Cholesterol also serves as a precursor for steroid hormones and bile acids.

The term "triglyceride(s)" ("TGs"), as used herein, incorporates its common usage. TGs consist of three fatty acid molecules esterified to a glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of LDL, VLDL and depressed levels of HDL).

Exemplary Primary Hyperlipidemia include, but are not limited to, the following: (1) Familial Hyperchylomicronemia, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

(2) Familial Hypercholesterolemia, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the

LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

(3) Familial Combined Hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

(4) Familial Defective Apolipoprotein B-100 is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

(5) Familial Dysbetaliproteinemia, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in moderate to severe elevations of serum TG and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

(6) Familial Hypertriglyceridemia, is a common inherited disorder in which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not cholesterol levels) and can often be associated with low plasma HDL levels.

Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of type 1 diabetes, type 2 diabetes, Cushing's syndrome, hypothyroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various .beta. blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%; saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity; and (4) non-genetic dyslipidemias.

The methods of the present invention can be used effectively in combination with one or more additional active diabetes agents depending on

the desired target therapy (see, e.g., Turner, N. et al. Prog. Drug Res. (1998) 51: 33-94; Haffner, S. Diabetes Care (1998) 21: 160-178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, e.g., Mahler, R., J. Clin. Endocrinol. Metab. (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al., Clin. Ther. (1997) 19: 16-26; Coniff, R. et al., Am. J. Med. (1995) 98: 443-451; and Iwamoto, Y. et al, Diabet. Med. (1996) 13 365-370; Kwiterovich, P. Am. J. Cardiol (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); vitamin B_3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II

antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms, complications, and disorders) with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPARα, PPARβ and PPARγ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulfate ester, DHEA-SO_4); antiglucocorticoids; TNFα inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Further provided by this invention are methods for treating obesity, as well as treating the complications of obesity, by administering a compound of the present invention. The antagonists can be identified, formulated, and administered similarly to the information described above. A FXR selective antagonist includes a partial agonist/antagonist or antagonist that exhibits about a two to about a ten-fold preference for FXR compared to another nuclear receptor such as, for example LXR α or β with respect to potency (IC_{50}, the concentration of compound that achieves 50% of the maximum reduction in the transcription activity achieved by the compound of interest observed in the presence of a sub-maximal concentration of FXR agonist) and/or efficacy (the maximum percent inhibition of transcription observed with the compound in question).

The terms "obese" and "obesity" refer to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/height^2 (m^2)). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia.

Obesity is also a known risk factor for the development of type 2 diabetes (See, e.g., Barrett-Conner, E., Epidemol. Rev. (1989) 11: 172-181; and Knowler, et al., Am. J Clin. Nutr. (1991) 53:1543-1551).

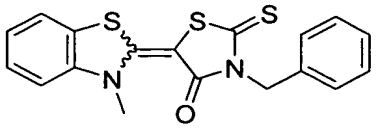
Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the methods can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

Another example of a combination therapy can be seen in treating cholestasis, where the compounds of the invention can be combined with Actigall (Ursodeoxycholic acid - UDCA), corticosteroids, anti-infective agents (Rifampin, Rifadin, Rimactane), anti-viral agents, Vitamin D, Vitamin A, phenobarbital, cholestyramine, UV light, antihistamines, oral opiate receptor antagonists and biphosphates, for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis. Dosage information for these agents is well known in the art.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the subject matter claimed herein.

EXAMPLE 1

A. Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxothiazolidin-4-one



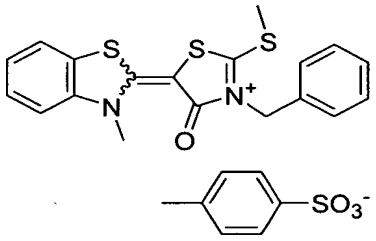
To a 100 mL flask was added anhydrous anisole (14 mL), 2-(methylthio)benzothiazole (10.0 g, 55.2 mmol) and methyl *p*-toluenesulfonate (12.5 mL, 82.7 mmol). After heating the mixture at 120 °C for 30 min, a

crystalline solid precipitated. Anisole (14 mL) was added and the mixture was further heated at 120 °C for 4 h.

After cooling to room temperature, the mixture was then transferred to a 1000 mL flask and diluted with anhydrous MeCN (200 mL). To the well-stirred mixture was added *N*-benzyl rhodanine (12.3 g, 55.1 mmol) and then dropwise TEA (12.5 mL, 90 mmol). The resulting yellow slurry was diluted with MeCN (200 mL) and stirred 2 h. The yellow precipitates were filtered under reduced pressure, washed first with MeCN (50 mL) and then MeOH (150 mL) to give the crude product.

To a three-neck 1 L flask fitted with a reflux condenser was added the crude product, acetone (100 mL) and MeOH (200 mL). The mixture was stirred under reflux for 15 min, cooled to room temperature, filtered under reduced pressure, washed with MeOH (100 mL) and dried under vacuum for 24 h to yield the title product (17.4 g, 85%) as a yellow solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 7.61 (1H, dd), 7.55 (2H, m), 7.44 (1H, m), 7.25-7.34 (4H, m), 7.21 (1H, d), 5.37 (2H, s), 3.91 (3H, s); MS(ESI): 371 (MH^+).

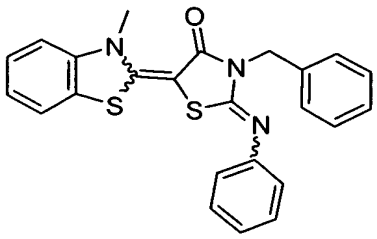
B. Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate



To a 200 mL flask was added 3-benzyl-5-(3-methylbenzothiazolin-2-ylidene)-2-thioxothiazolidin-4-one (5.00 g, 13.5 mmol), methyl *p*-toluenesulfonate (7.34 mL, 48.6 mmol) and anhydrous DMF(40 mL). After heating at 120 °C for 3 h, the mixture was allowed to cool to 60 °C, transferred to a 1 L flask and diluted with acetone (400 mL). After cooling to room temperature, the precipitate was filtered under reduced pressure, washed first with acetone (50 mL) and then Et_2O (100 mL), and dried under vacuum for 12 h to give the title product (6.25 g, 83%) as a yellow crystalline solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 7.83 (1H, d), 7.75

(2H, m), 7.59-7.66 (2H, m), 7.50 (1H, m), 7.37-7.43 (5H, m), 7.06 (2H, d), 5.31 2H, s), 4.52 (3H, s), 3.22 (3H, s), 2.28 (3H, s).

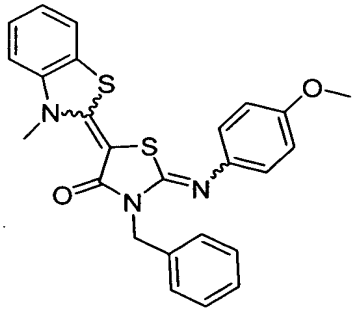
C. Preparation of 3-benzyl-5-(3-m thyl-3*H*-benzothiazol-2-ylidene)-2-phenylimino-thiazolidine-4-one



To an 8 mL vial was added 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate (100 mg, 0.18 mmol), aniline (16 μL, 0.18 mmol) and anhydrous MeCN (1 mL). After warming the mixture to 50°C, TEA (0.10 mL, 0.56 mmol) was added and continued heating the mixture at 50 °C for 12 h. After cooling to room temperature, the resulting precipitates were filtered under reduced pressure, washed with MeCN (2 mL) and dried under vacuum to yield the title product (22.3 mg, 29%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.59 (2H, m), 7.48 (1H, dd), 7.26-7.39 (6H, m), 7.10-7.18 (2H, m) 7.01 (3H, m), 5.16 (2H, s), 3.71 (3H, s); MS(ESI): 430 (MH^+).

EXAMPLE 2

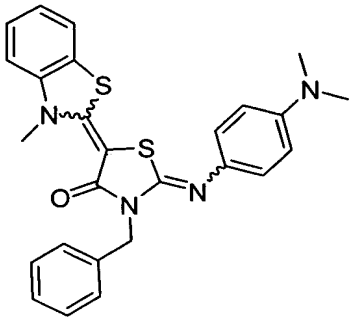
Preparation of 3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one.



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-anisidine. ^{1}H-NMR ($CDCl_3$): δ 7.58 (2H, d), 7.48 (1H, d), 7.26-7.35 (4H, m), 7.15 (1H, t), 7.01 (1H, d), 6.96 (2H, d), 6.90 (2H, d), 5.16 (2H, s), 3.82 (3H, s), 3.73 (3H, s); MS(ESI): 460 (MH^+).

EXAMPLE 3

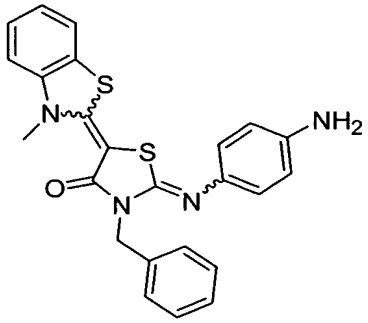
Preparation of 3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylid ne)thiazolidine-4-on .



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *N,N*-dimethyl-1,4-phenylendiamine. ^{1}H-NMR ($CDCl_3$): δ 7.59 (2H, d), 7.47 (1H, d), 7.24-7.35 (4H, m), 7.14 (1H, t), 6.99 (1H, d), 6.95 (2H, dd), 6.76 (2H, dd), 5.15 (2H, s), 3.73 (3H, s), 2.95 (6H, s); MS(ESI): 473 (MH^+).

EXAMPLE 4

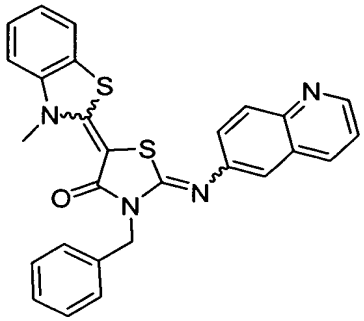
Preparation of 2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one.



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,4-phenylenediamine. ^{1}H-NMR ($CDCl_3$): δ 7.58 (2H, m), 7.47 (1H, dd), 7.27-7.34 (4H, m), 7.14 (1H, m), 6.99 (1H, d), 6.85 (2H, dd), 6.70 (2H, dd), 5.14 (2H, s), 3.72 (3H, s), 3.60 (2H, br); MS(ESI): 445 (MH^+).

EXAMPLE 5

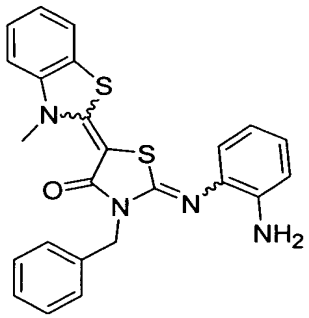
Preparation f 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 6-aminoquinoline. ^{1}H-NMR ($CDCl_3$): δ 8.84 (1H, dd), 8.09 (2H, d), 7.62 (2H, m), 7.50 (1H, d), 7.43 (1H, dd), 7.27-7.40 (6H, m), 7.16 (1H, m), 7.01 (1H, d), 5.20 (2H, s), 3.69 (3H, s); MS(ESI): 481 (MH^+).

EXAMPLE 6

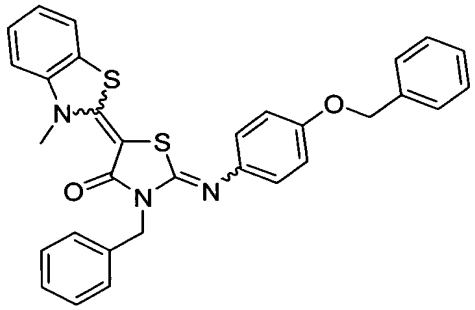
Preparation of 2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,2-phenylenediamine. ^{1}H-NMR ($CDCl_3$): δ 7.48-7.56 (3H, m), 7.30-7.36 (3H, m), 7.26-29 (1H, m), 7.17 (1H, t), 7.03 (1H, d), 6.91-6.99 (2H, m), 6.69-6.77 (2H, m), 5.19 (2H, s), 3.75 (3H, s), 3.49 (2H, s); MS(ESI): 445 (MH^+).

EXAMPLE 7

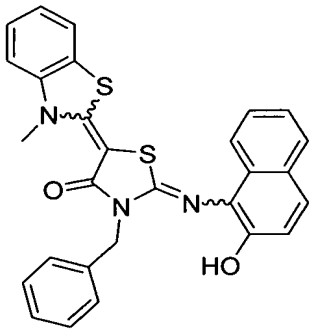
Preparation of 3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-benzyloxyaniline. ^{1}H-NMR ($CDCl_3$): δ 7.58 (2H, d), 7.43-7.50 (3H, m), 7.40 (2H, t), 7.26-7.36 (5H, m), 7.15 (1H, t), 6.93-7.03 (5H, m), 5.14 (2H, s), 5.07 (2H, s), 3.73 (3H, s); MS(ESI): 536 (MH^+).

EXAMPLE 8

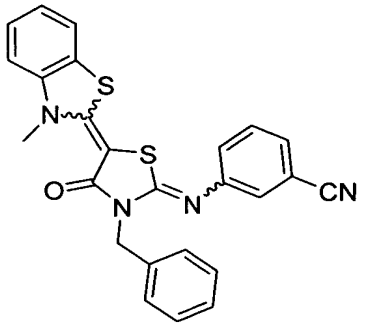
Preparation of 3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-amino-2-naphthol hydrochloride. ^{1}H-NMR ($CDCl_3$): δ 7.79 (1H, d), 7.56-7.64 (3H, m), 7.51 (2H, t), 7.28-7.44 (6H, m), 7.21 (1H, d), 7.18 (1H, t), 6.99 (1H, d), 5.34 (2H, s), 5.00 (1H, s), 3.57 (3H, s); MS(ESI): 496 (MH^+).

EXAMPLE 9

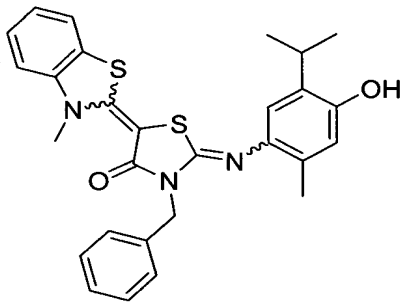
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminobenzonitrile. ^{1}H-NMR (DMSO-d_6): δ 7.72 (1H, d), 7.54 (2H, d), 7.23-7.41 (9H, m), 7.16-7.22 (1H, m), 5.02 (2H, s), 3.74 (3H, s); MS(ESI): 455 (MH^+).

EXAMPLE 10

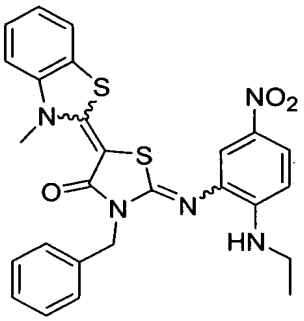
Preparation of 3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminothymol hydrochloride. ^{1}H-NMR ($CDCl_3$): δ 7.55-7.60 (2H, m), 7.48 (1H, d), 7.26-7.34 (4H, m), 7.14 (1H, m), 6.99 (1H, d), 6.76 (1H, s), 6.62 (1H, s), 5.17 (2H, s), 4.49 (1H, s), 3.71 (3H, s), 3.17 (1H, m), 1.96 (3H, s), 1.24 (6H, d); MS(ESI): 502 (MH^+).

EXAMPLE 11

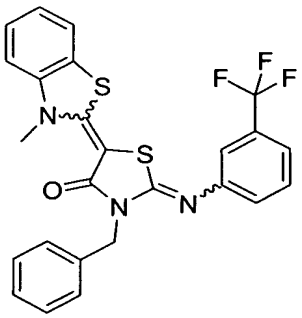
Preparation of 3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-m thyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with N^1-ethyl-4-nitrobenzene-1,2-diamine. ^{1}H-NMR ($CDCl_3$): δ 7.98 (1H, dd), 7.93 (1H, d), 7.55 (1H, d), 7.44 (2H, d), 7.19-7.42 (6H, m), 7.11 (1H, d), 6.46 (1H, d), 5.20 (2H, s), 4.55 (1H, br), 3.83 (3H, s), 3.07 (2H, m), 1.05 (3H, t); MS(ESI): 518 (MH^+).

EXAMPLE 12

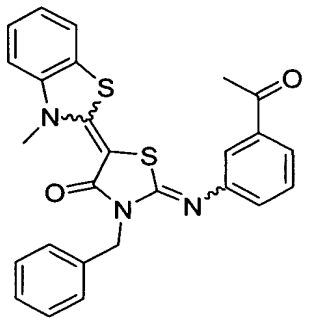
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-(trifluoromethyl)aniline. ^{1}H-NMR ($CDCl_3$): δ 7.57 (2H, m), 7.50 (1H, d), 7.46 (1H, t), 7.24-7.42 (6H, m), 7.15-7.21 (2H, m), 7.03 (1H, d), 5.15 (2H, s), 3.73 (3H, s); MS(ESI): 498 (MH^+).

EXAMPLE 13

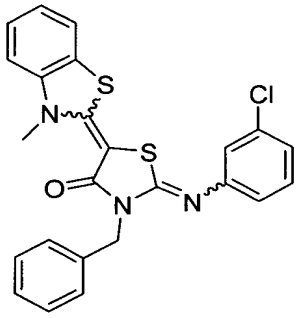
Preparation of 2-(3-acetylph nylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3'-aminoacetophenone. ^{1}H-NMR ($CDCl_3$): δ 7.72 (1H, m), 7.56-7.60 (3H, m), 7.50 (1H, dd), 7.45 (1H, t), 7.27-7.37 (4H, m), 7.21 (1H, ddd), 7.17 (1H, m), 7.02 (1H, d), 5.16 (2H, s), 3.72 (3H, s), 2.61 (3H, s); MS(ESI): 472 (MH^+).

EXAMPLE 14

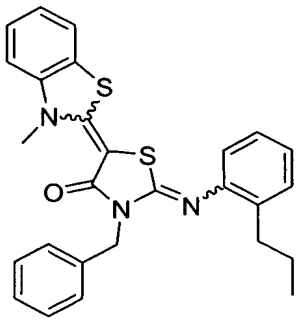
Preparation of 3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-chloroaniline. ^{1}H-NMR ($CDCl_3$): δ 7.54-7.58 (2H, m), 7.49 (1H, dd), 7.26-7.36 (5H, m), 7.17 (1H, m), 7.09 (1H, ddd), 7.03 (1H, d), 7.01 (1H, t), 6.89 (1H, ddd), 5.13 (2H, s), 3.74 (3H, s); MS(ESI): 464 (MH^+).

EXAMPLE 15

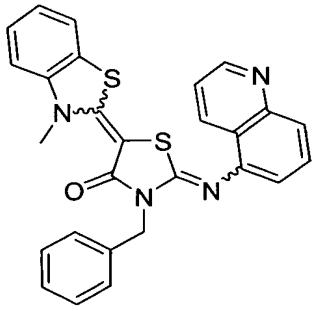
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-propyl-phenylimino)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 2-propylaniline. ^{1}H-NMR ($CDCl_3$): δ 7.49 (1H, d), 7.27-7.37 (4H, m), 7.12-7.23 (3H, m), 7.06 (1H, m), 7.00 (1H, d), 6.92 (1H, d), 5.17 (2H, s), 3.71 (3H, s), 2.37 (2H, t), 1.42 (2H, s), 0.79 (3H, t); MS(ESI): 472 (MH^+).

EXAMPLE 16

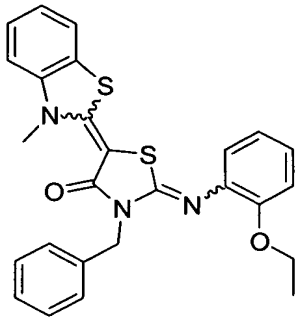
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoquinoline. ^{1}H-NMR ($CDCl_3$): δ 8.86 (1H, d), 8.02 (1H, d), 7.81 (1H, d), 7.68 (1H, t), 7.42-7.50 (3H, m), 7.25-7.35 (5H, m), 7.20 (1H, d), 7.12 (1H, t), 7.07 (1H, d), 5.19 (2H, s), 3.67 (3H, s); MS(ESI): 481 (MH^+).

EXAMPLE 17

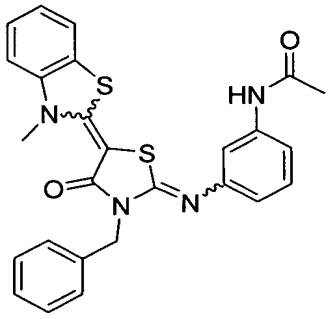
Preparation of 3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *o*-phenetidine. ^{1}H-NMR ($CDCl_3$): δ 7.66 (2H, m), 7.46 (2H, d), 7.24-7.34 (3H, m), 7.07-7.16 (2H, m), 6.94-7.00 (4H, m), 5.19 (2H, s), 4.01 (2H, q), 3.69 (3H, s), 1.36 (3H, t); MS(ESI): 474 (MH^+).

EXAMPLE 18

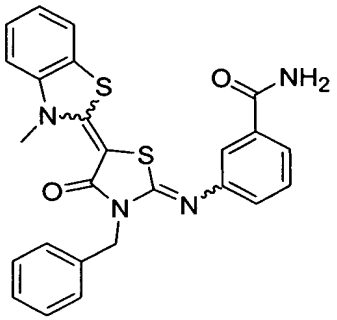
Preparation of *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3'-aminoacetanilide. ^{1}H-NMR ($CDCl_3$): δ 7.57 (2H, d), 7.48 (1H, d), 7.27-7.39 (6H, m), 7.15 (2H, m), 7.06 (1H, br s), 7.01 (1H, d), 6.76 (1H, d), 5.14 (2H, s), 3.72 (3H, s), 2.18 (3H, s); MS(ESI): 487 (MH^+).

EXAMPLE 19

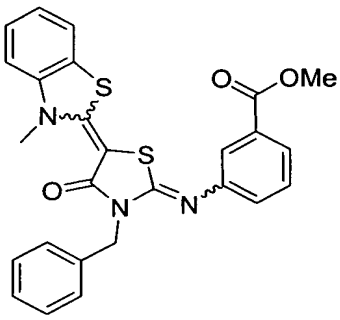
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminobenzamide. ^{1}H-NMR (DMSO-d_6): δ 7.98 (1H, br s), 7.74 (1H, d), 7.62 (1H, d), 7.34-7.48 (9H, m), 7.30 (1H, m), 7.21 (1H, m), 7.12 (1H, d), 5.06 (2H, s), 3.75 (3H, s); MS(ESI): 473 (MH^+).

EXAMPLE 20

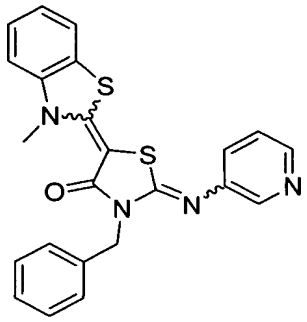
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with methyl 3-aminobenzoate. ^{1}H-NMR ($CDCl_3$): δ 7.80 (1H, m), 7.68 (1H, m), 7.56-7.60 (2H, m), 7.49 (1H, dd), 7.42 (1H, m), 7.27-7.36 (4H, m), 7.14-7.20 (2H, m), 7.01 (1H, d), 5.16 (2H, s), 3.92 (3H, s), 3.71 (3H, s); MS(ESI): 488 (MH^+).

EXAMPLE 21

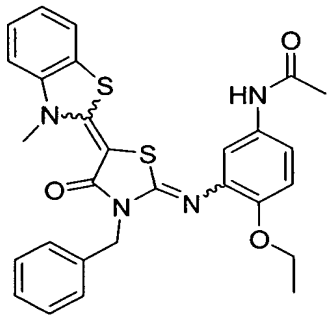
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminopyridine. ^{1}H-NMR ($CDCl_3$): δ 8.37 (1H, dd), 8.35 (1H, dd), 7.56-7.60 (2H, m), 7.51 (1H, dd), 7.27-7.37 (6H, m), 7.18 (1H, m), 7.04 (1H, d), 5.16 (2H, s), 3.73 (3H, s); MS(ESI): 431 (MH^+).

EXAMPLE 22

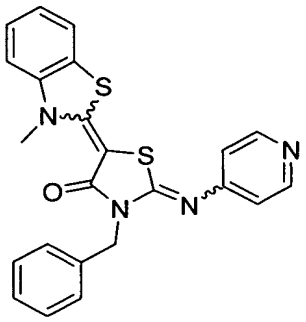
Preparation of *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethoxyphenyl}acetamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *N*-(4-amino-3-ethoxyphenyl)acetamide. ^{1}H-NMR ($CDCl_3$): δ 7.63 (2H, d), 7.48 (1H, d), 7.28-7.36 (5H, m), 7.15 (1H, t), 7.10 (1H, s), 7.00 (1H, d), 6.96 (1H, d), 6.91 (1H, d), 5.18 (2H, s), 3.97 (2H, q), 3.70 (3H, s), 2.16 (3H, s), 1.33 (3H, t); MS(ESI): 531 (MH^+).

EXAMPLE 23

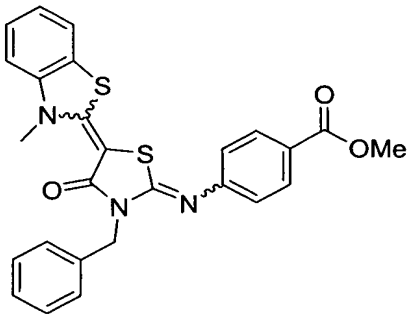
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminopyridine. ^{1}H-NMR ($CDCl_3$): δ 8.53 (2H, dd), 7.56 (2H, m), 7.52 (1H, dd), 7.28-7.38 (4H, m), 7.19 (1H, m), 7.06 (1H, d), 6.93 (2H, dd), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 431 (MH^+).

EXAMPLE 24

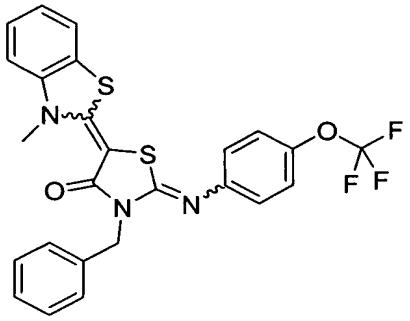
Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with methyl 4-aminobenzoate. ^{1}H-NMR ($CDCl_3$): δ 8.04 (2H, m), 7.58 (2H, m), 7.50 (1H, d), 7.27-7.38 (4H, m), 7.17 (1H, t), 7.01-7.08 (3H, m), 5.15 (2H, s), 3.92 (3H, s), 3.72 (3H, s); MS(ESI): 488 (MH^+).

EXAMPLE 25

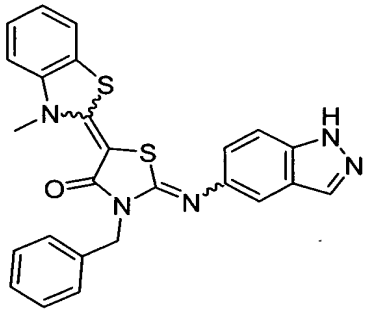
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoro-methoxy)phenylimino]thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-(trifluoromethoxy)aniline. ^{1}H-NMR ($CDCl_3$): δ 7.57 (2H, m), 7.50 (1H, dd), 7.27-7.36 (4H, m), 7.14-7.22 (3H, m), 7.03 (1H, d), 7.00 (2H, dd), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 514 (MH^+).

EXAMPLE 26

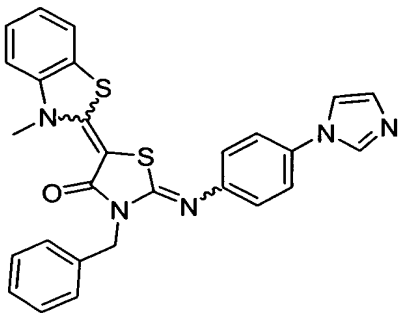
Preparation of 3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoindazole. ^{1}H-NMR ($CDCl_3$): δ 10.05 (1H, br s), 8.08 (1H, d), 7.64-7.67 (2H, m), 7.51-7.55 (2H, m), 7.32-7.41 (5H, m), 7.20 (1H, m), 7.14 (1H, dd), 7.04 (1H, d), 5.23 (2H, s), 3.74 (3H, s); MS(ESI): 470 (MH^+).

EXAMPLE 27

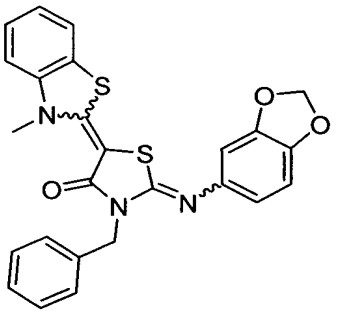
Preparation of 3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-(1*H*-imidazol-1-yl)aniline. ^{1}H-NMR ($CDCl_3$): δ 7.93 (1H, s), 7.66 (2H, d), 7.58 (1H, d), 7.35-7.46 (7H, m), 7.29 (1H, s), 7.25 (1H, t), 7.18 (2H, m), 7.11 (1H, d), 5.24 (2H, s), 3.82 (3H, s); MS(ESI): 496 (MH^+).

EXAMPLE 28

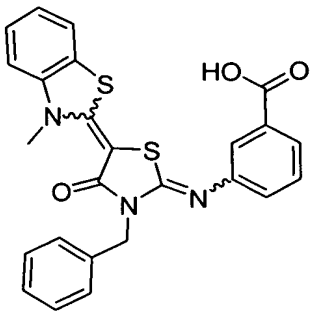
Preparation of 2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3,4-(methylenedioxy)aniline. ^{1}H-NMR ($CDCl_3$): δ 7.56-7.60 (2H, m), 7.49 (1H, dd), 7.28-7.36 (4H, m), 7.16 (1H, m), 7.02 (1H, d), 6.80 (1H, d), 6.56 (1H, d), 6.48 (1H, dd), 5.98 (2H, s), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 474 (MH^+).

EXAMPLE 29

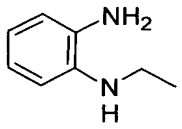
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-yliden amino]benzoic acid



An aqueous solution of lithium hydroxide (1 M, 5 mL) was added to a solution of compound I-20 (0.13 g, 0.27 mmol) in THF (20 mL). After stirring at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was acidified with hydrochloric acid (1 M, 10 mL) and extracted with EtOAc. The combined organic extracts were dried (anhydrous magnesium sulfate), concentrated under reduced pressure and chromatographed (silica gel, MeOH/DCM, 1:19) to yield the title compound (0.12 g, 95%) as a yellow solid. ^{1}H-NMR (MeOD-d_3): δ 7.81 (1H, d), 7.63-7.68 (2H, m), 7.55 (1H, d), 7.50 (2H, d), 7.44 (1H, t), 7.31-7.40 (3H, m), 7.28 (1H, d), 7.16-7.23 (3H, m), 5.15 (2H, s), 3.79 (3H, s); MS(ESI): 474 (MH^+).

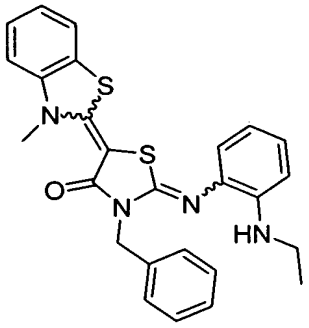
EXAMPLE 30

Preparation of *N*-ethyl-1,2-phenylenediamine



N-Ethyl-2-nitroaniline (0.97 g, 5.8 mmol) was dissolved in EtOAc (60 mL) and placed in a closed vessel. 10% Pd/C (0.4 g, 7 mol%) was added and the mixture was hydrogenated under 50 psi H_2 for 2 h. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to yield the title product (0.79 g, 99%) as a brown liquid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 6.83 (1H, m), 6.64-6.74 (3H, m), 3.29 (3H, br s), 3.15 (2H, q), 1.30 (3H, t); TLC (2:98 MeOH/DCM R_f 0.24).

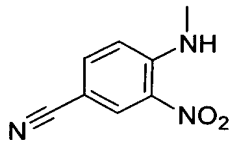
Preparation of 3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzthiazol-2-ylidene)thiazolidine-4-one



The title compound was then prepared in a manner similar to that described in Example 1 by replacing aniline with *N*-ethyl-1,2-phenylenediamine. ^{1}H-NMR ($CDCl_3$): δ 7.47-7.54 (3H, m), 7.30-7.37 (3H, m), 7.28 (1H, m), 7.17 (1H, t), 7.00-7.06 (2H, m), 6.96 (1H, dd), 6.64 (1H, m), 6.60 (1H, d), 5.19 (2H, s), 3.76 (3H, s), 3.68 (1H, br s), 3.01 (2H, q), 1.05 (3H, t); MS(ESI): 473 (MH^+).

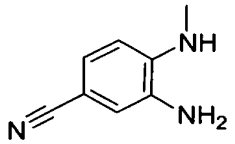
EXAMPLE 31

Preparation of 4-methylamino-3-nitrobenzonitrile



4-Fluoro-3-nitrobenzonitrile (0.25 g, 1.5 mmol) was cautiously added to a solution of methylamine (2.0 M, 5.0 mL) in THF. The mixture was stirred at room temperature for 8 h, concentrated under reduced pressure, and chromatographed (silica gel, DCM) to give the title product (0.18 g, 68%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.52 (1H, d), 8.41 (1H, br s), 7.64 (1H, dd), 6.92 (1H, d), 3.10 (3H, d).

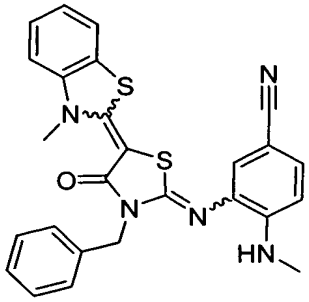
Preparation of 3-amino-4-(methylamino)benzonitrile



4-Methylamino-3-nitrobenzonitrile (0.18 g, 1.0 mmol) was dissolved in EtOAc (10 mL) and placed in a closed vessel. 10% Pd/C (50 mg, 5 mol%) was added and the mixture was hydrogenated *via* a hydrogen-filled balloon

that was affixed to the vessel. After 2 h the mixture was filtered through celite and the filtrate was concentrated under reduced pressure to yield the title product (0.14 g, 93%) as an off-white solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 7.19 (1H, dd), 6.92 (1H, d), 6.57 (1H, d), 4.04 (1H, br s), 3.30 (2H, br s), 2.91 (3H, br s); TLC (5:95 MeOH/DCM R_f 0.33).

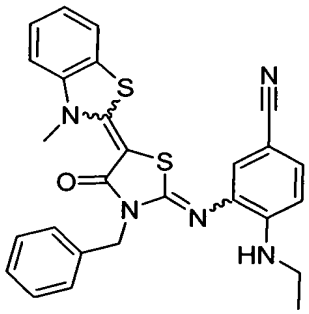
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile



The title compound was then prepared in a manner similar to that described in Example 1 by replacing aniline with 3-amino-4-(methylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.55 (1H, d), 7.42-7.47 (2H, m), 7.34-7.41 (3H, m), 7.28-7.34 (2H, m), 7.21 (1H, m), 7.18 (1H, d), 7.11 (1H, d), 6.45 (1H, d), 5.17 (2H, s), 4.15 (1H, br s), 3.83 (3H, s), 2.63 (3H, br s); MS(ESI): 484 (MH^+).

EXAMPLE 32

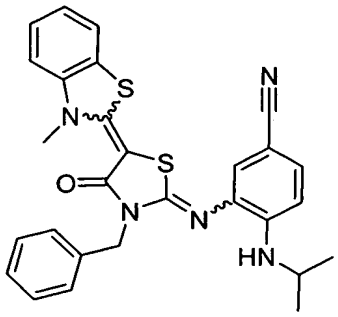
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with ethylamine. ^{1}H-NMR ($CDCl_3$): δ 7.54 (1H, d), 7.41-7.46 (2H, m), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.49 (1H, d), 5.18 (2H, s), 4.23 (1H, t), 3.83 (3H, s), 3.01 (2H, m), 1.02 (3H, t); MS(ESI): 498 (MH^+).

EXAMPLE 33

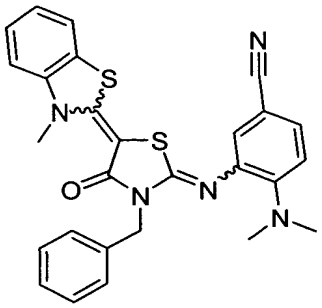
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)b nzonitril



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with isopropylamine. ^{1}H-NMR ($CDCl_3$): δ 7.54 (1H, d), 7.45 (2H, d), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.53 (1H, d), 5.18 (2H, s), 4.29 (1H, d), 3.83 (3H, s), 3.54 (1H, m), 1.02 (6H, d); MS(ESI): 512 (MH^+).

EXAMPLE 34

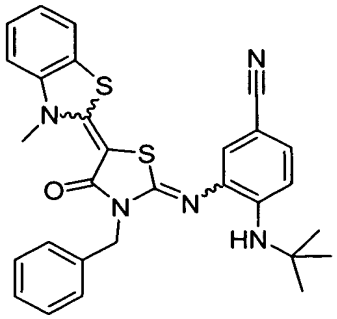
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with dimethylamine. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.53 (3H, m), 7.27-7.37 (5H, m), 7.18 (1H, t), 7.13 (1H, d), 7.06 (1H, d), 6.85 (1H, d), 5.18 (2H, s), 3.76 (3H, s), 2.68 (6H, s); MS(ESI): 498 (MH^+).

EXAMPLE 35

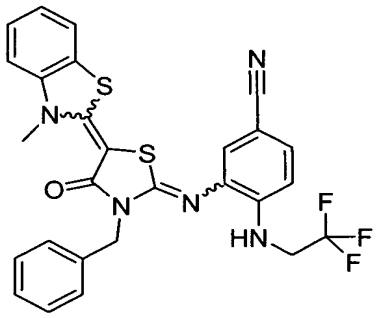
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-b nzothiazol-2-yliden)-4-oxothiazolidin-2-ylideneamino]-4-(*tert*-butylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with *tert*-butylamine. ^{1}H-NMR ($CDCl_3$): δ 7.54 (1H, d), 7.44 (2H, d), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.80 (1H, d), 5.18 (2H, s), 4.67 (1H, br s), 3.83 (3H, s), 1.22 (9H, s); MS(ESI): 526 (MH^+).

EXAMPLE 36

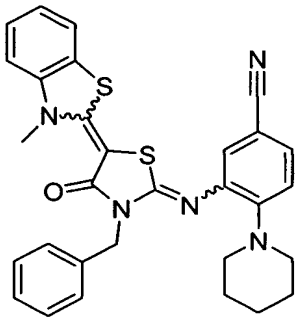
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile.



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 2,2,2-trifluoroethylamine. ^{1}H-NMR ($CDCl_3$): δ 7.57 (1H, d), 7.27-7.44 (8H, m), 7.23 (1H, t), 7.14 (1H, d), 6.62 (1H, d), 5.17 (2H, s), 4.49 (1H, t), 3.86 (3H, s), 3.50 (2H, m); MS(ESI): 552 (MH^+).

EXAMPLE 37

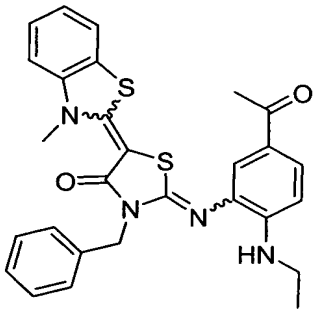
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with piperidine. ^{1}H-NMR ($CDCl_3$): δ 7.50-7.54 (3H, m), 7.27-7.37 (5H, m), 7.18 (1H, t), 7.15 (1H, d), 7.05 (1H, d), 6.92 (1H, d), 5.17 (2H, s), 3.75 (3H, s), 2.98 (4H, m), 1.44 (6H, m); MS(ESI): 538 (MH^+).

EXAMPLE 38

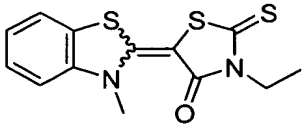
Preparation of 2-[5-acetyl-2-(ethylamino)phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with ethylamine and by replacing 4-fluoro-3-nitrobenzonitrile with 4'-chloro-3'-nitroacetophenone. ^{1}H-NMR ($CDCl_3$): δ 7.68 (1H, dd), 7.65 (1H, d), 7.53 (1H, d), 7.45-7.49 (2H, m), 7.32-7.38 (3H, m), 7.28-7.31 (1H, m), 7.19 (1H, m), 7.06 (1H, d), 6.52 (1H, d), 5.19 (2H, s), 4.24 (1H, t), 3.78 (3H, s), 3.06 (2H, m), 2.51 (3H, s), 1.05 (3H, t); MS(ESI): 515 (MH^+).

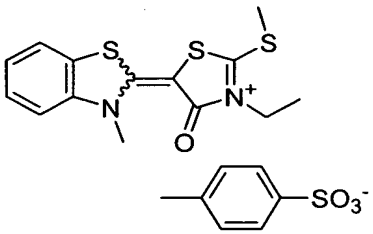
EXAMPLE 39

Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-yliden)-2-thioxothiazolidin-4-one



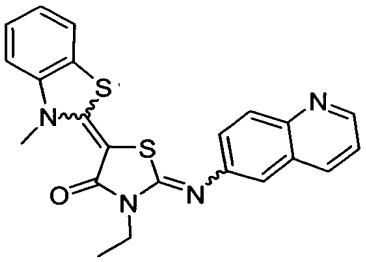
The title compound was prepared in a manner similar to that described in Example 1 by replacing *N*-benzyl rhodanine with *N*-ethyl rhodanine. ^{1}H-NMR ($CDCl_3$): δ 7.63 (1H, d), 7.45 (1H, m), 7.30 (1H, m), 7.22 (1H, d), 4.24 (2H, q), 3.91 (3H, s), 1.32 (3H, t); MS(ESI): 309 (MH^+).

Preparation 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate



The title compound was prepared from 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxothiazolidin-4-one and methyl *p*-toluenesulfonate in a manner similar to that described in Example 1. ^{1}H-NMR ($CDCl_3$): δ 7.82 (1H, d), 7.77 (2H, d), 7.58-7.66 (2H, m), 7.49 (1H, m), 7.08 (2H, d), 4.52 (3H, s), 4.21 (2H, q), 3.29 (3H, s), 2.29 (3H, s), 1.45 (3H, t).

Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidin-4-one

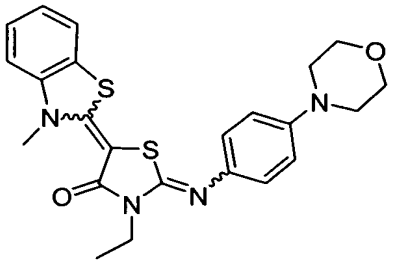


The title compound was prepared from 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate and 6-aminoquinoline in a manner similar to that described in Example 1. ^{1}H-NMR ($CDCl_3$): δ 8.85 (1H, dd), 8.11 (1H, d), 8.10 (1H, d), 7.51 (1H, dd) 7.46

(1H, dd), 7.40 (1H, d), 7.38 (1H, dd), 7.32 (1H, m), 7.16 (1H, m), 7.01 (1H, d), 4.10 (2H, q), 3.70 (3H, s), 1.41 (3H, t); MS(ESI): 419 (MH^+).

EXAMPLE 40

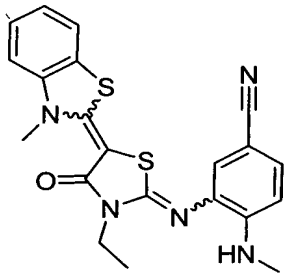
Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-yl-phenylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 4-morpholin-4-ylaniline. ^{1}H-NMR ($CDCl_3$): δ 7.49 (1H, dd), 7.31 (1H, m), 7.15 (1H, m), 6.91-7.02 (5H, m), 4.03 (2H, q), 3.88 (4H, m), 3.73 (3H, s), 3.17 (4H, m), 1.36 (3H, t); MS(ESI): 453 (MH^+).

EXAMPLE 41

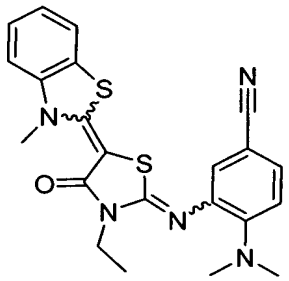
Preparation of 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(methylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.53 (1H, d), 7.36 (1H, m), 7.36 (1H, dd), 7.25 (1H, m), 7.20 (1H, m), 7.09 (1H, d), 6.60 (1H, d), 4.86 (1H, q), 4.07 (2H, q), 3.81 (3H, s), 2.92 (3H, d), 1.37 (3H, t); MS(ESI): 422 (MH^+).

EXAMPLE 42

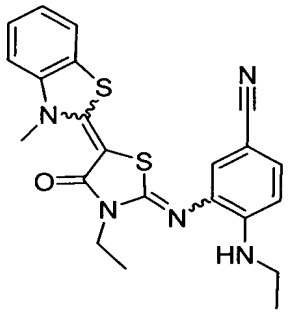
Preparation of 4-dimethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(dimethylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.52 (1H, dd), 7.34 (1H, m), 7.34 (1H, dd), 7.20 (1H, d), 7.18 (1H, m), 7.06 (1H, d), 6.92 (1H, d), 4.08 (2H, q), 3.76 (3H, s), 2.90 (6H, s), 1.38 (3H, t); MS(ESI): 436 (MH^+).

EXAMPLE 43

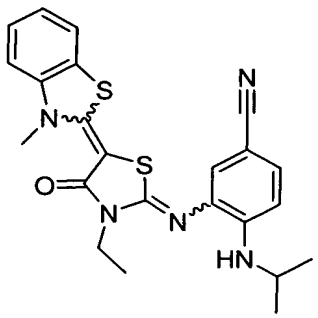
Preparation of 4-ethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(ethylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.53 (1H, d), 7.32-7.40 (2H, m), 7.26 (1H, m), 7.20 (1H, m), 7.10 (1H, d), 6.60 (1H, d), 4.75 (1H, t), 4.08 (2H, q), 3.81 (3H, s), 3.22 (2H, m), 1.37 (3H, t), 1.29 (3H, t); MS(ESI): 436 (MH^+).

EXAMPLE 44

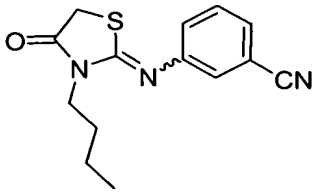
Preparation of 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-yliden amino]-4-(isopropylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(isopropylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.53 (1H, dd), 7.36 (1H, m), 7.32 (1H, dd), 7.25 (1H, d), 7.20 (1H, m), 7.10 (1H, d), 6.60 (1H, d), 4.74 (1H, d), 4.08 (2H, q), 3.81 (3H, s), 3.67 (1H, m), 1.37 (3H, t), 1.25 (6H, d); MS(ESI): 450 (MH^+).

EXAMPLE 45

Preparation of 3-(3-butyl-4-oxothiazolidin-2-ylideneamino)benzonitrile

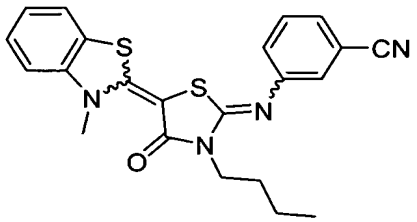


To a 250 mL flask was added 3-aminobenzonitrile (0.59 g, 5.0 mmol), $CHCl_3$ (25 mL) and saturated sodium bicarbonate (25 mL). To the well-stirred mixture was added dropwise thiophosgene (0.39 mL, 5.1 mmol). After 2h butylamine (0.50 mL, 5.1 mmol) was added dropwise and stirred 1 h. The reaction mixture was then extracted with $CHCl_3$, concentrated under reduced pressure, and chromatographed (silica gel, 2:98 MeOH/DCM) to yield 1-butyl-3-(3-cyanophenyl)thiourea (1.02 g, 87%) as a white solid: TLC (2:98 MeOH/DCM R_f 0.47).

To a 100 mL flask was added anhydrous EtOH (25 mL), 1-butyl-3-(3-cyanophenyl)thiourea (0.99 g, 4.2 mmol), ethyl chloroacetate (0.51 mL, 5.0 mmol), and anhydrous pyridine (0.5 mL, 5 mmol). After heating under reflux 16 h, the product mixture was concentrated under reduced pressure and

chromatographed (silica gel, 2:98 MeOH/DCM) to afford the title product (0.78 g, 67%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 7.40-7.47 (2H, m), 7.25 (1H, m), 7.19 (1H, m), 3.84 (2H, t), 3.84 (2H, s), 1.69 (2H, m), 1.39 (2H, m), 0.97 (3H, t); MS(ESI): 274 (MH^+).

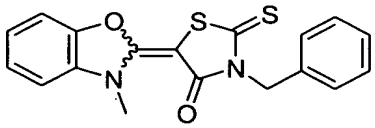
Preparation of 3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



To a 8 mL vial was added 3-(3-butyl-4-oxothiazolidin-2-ylideneamino)benzonitrile (55 mg, 0.20 mmol), 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate (73 mg, 0.20 mmol), anhydrous MeCN (2 mL) and TEA (70 μL, 0.50 mmol). The reaction mixture was first warmed to 50 °C and the resulting solution was allowed to stir at room temperature for 16 h. The product mixture was concentrated under reduced pressure, chromatographed (silica gel, 1:99 MeOH/DCM) and then recrystallized from MeCN to give the title product (11.8 mg) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.52 (1H, dd), 7.38-7.48 (2H, m), 7.32-7.37 (2H, m), 7.25 (1H, m), 7.18 (1H, m), 7.06 (1H, d), 3.96 (2H, t), 3.75 (3H, s), 1.77 (2H, m), 1.44 (2H, m), 0.98 (3H, t); MS(ESI): 421 (MH^+).

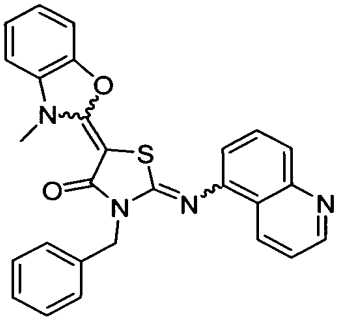
EXAMPLE 46

Preparation of 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-thioxothiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 2-mercaptobenzoxazole. ^{1}H-NMR ($CDCl_3$): δ 7.49 (2H, d), 7.24-7.41 (6H, m), 7.18 (1H, d), 5.31(2H, s), 4.17 (3H, s); MS(ESI): 377 (MNa^+).

Preparation of 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidin-4-one

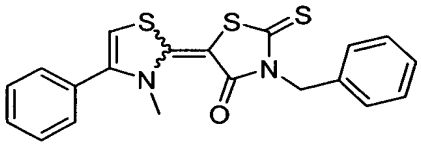


To a 10 mL flask was added 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-thioxothiazolidin-4-one (100 mg, 0.28 mmol), anhydrous $CHCl_3$ (2 mL) and methyl *p*-toluenesulfonate (53 μL, 0.35 mmol). After heating at reflux 10 min, the reaction mixture was heated at 120 °C for 2 h to yield a red oil. The desired intermediate, 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate, was not isolated successfully in previous experiments similar to Example 1 and, thus, the crude reaction mixture was diluted with anhydrous $CHCl_3$ (4 mL) and used without purification in the next step.

To a 8 mL vial was added the crude reaction mixture (2 mL) and 5-aminoquinoline (29 mg, 0.20 mmol). After warming the mixture to 55 °C, TEA (0.10 mL, 0.56 mmol) was added and the mixture was heated at 60 °C for 16 h. After cooling to room temperature, the resulting product mixture was concentrated under reduced pressure and chromatographed (silica gel, 2:98 MeOH/DCM) to yield the title product (21 mg) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.86 (1H, dd), 7.97 (1H, dd), 7.85 (1H, d), 7.66 (1H, dd), 7.56 (2H, m), 7.30-7.42 (3H, m), 7.19-7.25 (3H, m), 7.11-7.17 (2H, m), 7.05 (1H, d), 5.24 (2H, s), 4.11 (3H, s); MS(ESI): 465 (MH^+).

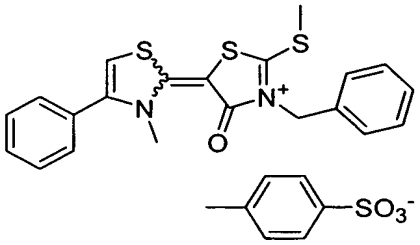
EXAMPLE 47

Preparation of 3'-benzyl-3-methyl-4-phenyl-2'-thioxo-2',3'-dihydro-3*H*-[2,5']bithiazol-yliden-4'-one



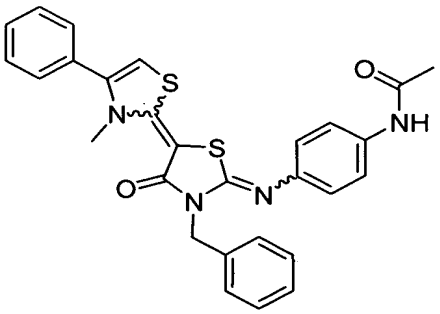
The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 2-mercapto-4-phenylthiazole. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.56 (5H, m), 7.34-7.38 (2H, m), 7.24-7.33 (3H, m), 6.54 (1H, s), 5.39 (2H, s), 3.68 (3H, s); MS(ESI): 397 (MH^+).

Preparation 3'-benzyl-3-methyl-2'-methylthio-4'-oxo-4-phenyl-3*H*,4'*H*-[2,5']bithiazol-yliden-3'-ium *p*-toluenesulfonate



The title compound was prepared from 3'-benzyl-3-methyl-4-phenyl-2'-thioxo-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one and methyl *p*-toluenesulfonate in a manner similar to that described in Example 1. ^{1}H-NMR ($CDCl_3$): δ 7.72 (2H, d), 7.49-7.56 (3H, m), 7.42-7.47 (2H, m), 7.36-7.41 (5H, m), 7.05 (2H, d), 6.99 (1H, s), 5.29 (2H, s), 4.26 (3H, s), 3.14 (3H, s), 2.29 (3H, s).

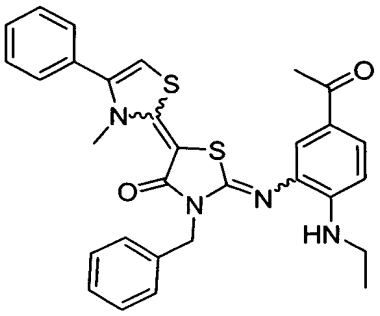
Preparation of *N*-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)phenyl]acetamide



The title compound was prepared from 3'-benzyl-3-methyl-2'-methylthio-4'-oxo-4-phenyl-3*H*,4'*H*-[2,5']bithiazolyliden-3'-ium *p*-toluenesulfonate and 4'-aminoacetanilide in a manner similar to that described in Example 1. ^{1}H-NMR ($CDCl_3$): δ 7.56 (2H, d), 7.42-7.47 (5H, m), 7.24-7.34 (5H, m), 7.12 (1H, s), 6.97 (2H, d), 6.30 (1H, s), 5.15 (2H, s), 3.49 (3H, s), 2.17 (3H, s); MS(ESI): 513 (MH^+).

EXAMPLE 48

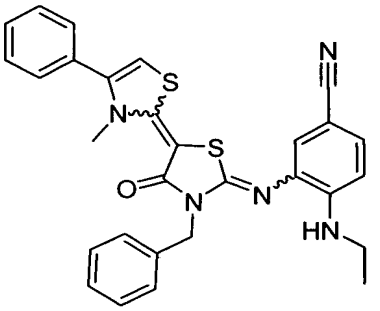
Preparation of 2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 47 by replacing 4'-aminoacetanilide with 3'-amino-4'-(ethylamino)acetophenone. ^{1}H-NMR ($CDCl_3$): δ 7.63-7.67 (2H, m), 7.44-7.48 (5H, m), 7.27-7.37 (5H, m), 6.50 (1H, d), 6.37 (1H, s), 5.20 (2H, s), 4.29 (1H, t), 3.55 (3H, s), 3.05 (2H, m), 2.49 (3H, s), 1.04 (3H, t); MS(ESI): 541 (MH^+).

EXAMPLE 49

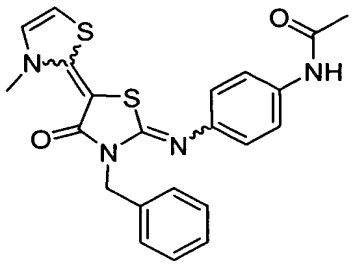
Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 47 by replacing 4'-aminoacetanilide with 3-amino-4-(ethylamino)benzonitrile. ^{1}H-NMR ($CDCl_3$): δ 7.46-7.50 (3H, m), 7.41-7.45 (2H, m), 7.23-7.40 (6H, m), 7.21 (1H, d), 6.47 (1H, d), 6.40 (1H, s), 5.18 (2H, s), 4.27 (1H, t), 3.59 (3H, s), 3.00 (2H, m), 1.01 (3H, t); MS(ESI): 524 (MH^+).

EXAMPLE 50

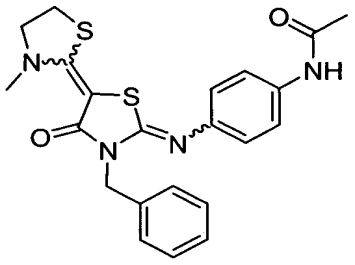
Preparation of *N*-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)phenyl]ac tamide



The title compound was prepared in a manner similar to that described in Example 47 by replacing 2-mercapto-4-phenylthiazole with 2-mercaptothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.55 (2H, d), 7.44 (2H, d), 7.24-7.33 (3H, m), 7.13 (1H, s), 6.95 (2H, d), 6.52 (1H, d), 6.37 (1H, d), 5.12 (2H, s), 3.68 (3H, s), 2.17 (3H, s); MS(ESI): 437 (MH^+).

EXAMPLE 51

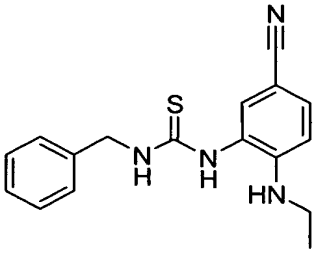
Preparation of *N*-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylidene-amino)phenyl]acetamide



The title compound was prepared in a manner similar to that described in Example 47 by replacing 2-mercapto-4-phenylthiazole with 2-methylthio-2-thiazoline. ^{1}H-NMR ($CDCl_3$): δ 7.53 (2H, d), 7.44 (2H, d), 7.23-7.32 (3H, m), 7.14 (1H, s), 6.93 (2H, d), 5.07 (2H, s), 3.63 (2H, t), 3.16 (3H, s), 3.09 (2H, t), 2.17 (3H, s); MS(ESI): 439 (MH^+).

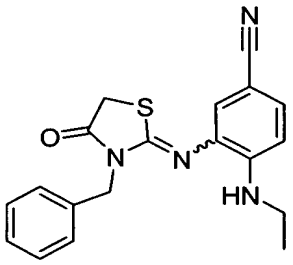
EXAMPLE 52

Preparation of 1-benzyl-3-(5-cyano-2-ethylaminophenyl)thiourea



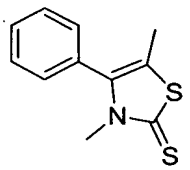
To a 100 mL flask was added 3-amino-4-(ethylamino)benzonitrile (1.0 g, 6.2 mmol), anhydrous THF (50 mL) and benzylisothiocyanate (0.92 g, 6.2 mmol). The reaction mixture was heated at 50 °C with stirring for 6 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to yield the title product (1.78 g, 93 %). ^{1}H-NMR ($CDCl_3$): δ 7.48 (1H, dd), 7.37 (1H, d), 7.31 (3H, m), 7.24 (1H, s), 7.18 (1H, br), 6.67 (1H, d), 5.95 (1H, br), 4.81 (2H, d), 4.68 (1H, br), 3.19 (2H, m), 1.23 (3H, t).

Preparation of 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzo-nitrile



To a 100 mL flask was added 1-benzyl-3-(5-cyano-2-ethylaminophenyl)thiourea (1.0 g, 3.2 mmol), anhydrous ethanol (40 mL), ethyl chloroacetate (0.39 g, 3.2 mmol) and then DBU (0.58 g, 3.8 mmol). The reaction was heated at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to afford the title product (0.98 g, 87 %). ^{1}H-NMR ($CDCl_3$): δ 7.38 (6H, m), 7.11 (1H, d), 6.50 (1H, d), 5.05 (2H, s), 3.96 (2H, s), 3.01 (2H, m), 1.03 (3H, t).

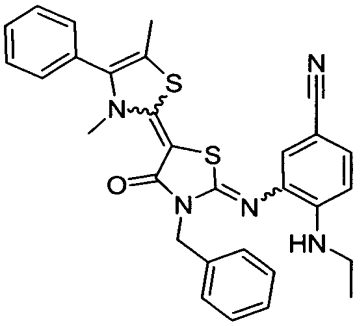
Preparation of 3,5-dimethyl-4-phenyl-3*H*-thiazole-2-thione



To a 100 mL flask was added freshly prepared triethylammonium methyldithiocarbamate (2.0 g, 9.5 mmol), anhydrous MeCN (50 mL), and 2-bromopropiophenone (2.04 g, 9.5 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting crude residue was treated with conc

H_2SO_4 (5 mL) with stirring at room temperature. After 20 min, the reaction mixture was diluted with water (75 mL) and then mixed with DCM (75 mL). The layers were separated and the aqueous layer extracted once more with DCM (75 mL). The combined organic layers were washed with water (3 x 50 mL) and then brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the title product (1.95 g, 92%) as an off - white solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 7.50 (2H, m), 7.27 (2H,m), 3.45 (3H, s), 2.06 (3H,s).

Preparation of 3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile



To an 8 mL vial was added 3,5-dimethyl-4-phenyl-3*H*-thiazole-2-thione (100 mg, 0.45 mmol), methyl *p*-toluenesulfonate (126 mg, 0.68 mmol) and anhydrous anisole (0.5 mL). The reaction was heated to 120 °C and stirred for 3h. The cooled reaction mixture was diluted with anhydrous MeCN (3 mL) and then treated with 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzonitrile (50 mg, 0.14 mmol) and TEA (70 μL, 0.50 mmol). The reaction mixture was warmed to 80 °C and the resulting solution was allowed to stir for 16 h. The product mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to yield the title product (48.3 mg, 64%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.40 (5H, m), 7.33 (2H,m), 7.25 (3H, m), 7.23 (2H, m), 6.46 (1H, d), 5.18 (2H, s), 4.28 (1H, m), 3.46 (3H, s), 2.99 (2H, m), 2.28 (3H, s), 1.01 (3H, t); MS(ESI): 538 (MH^+).

EXAMPLE 53

Time Resolved Fluorescence Resonanc Energy Transfer (TR-FRET) Assay

The FRET assay was performed by incubating 8 nM of GST-FXR-LBD, 8 nM of Europium-labeled anti-GST antibody (Wallac), 16 nM biotin-SRC-1 peptide [5'-biotin-CPSSHSSLTERHKILHRLLQEGSPS-CONH2], 20 nM APC-SA [allophycocyanin conjugated streptavidin] (Wallac) in FRET assay buffer (20 mM KH_2PO_4/K_2HPO_4 (pH 7.3), 150 mM NaCl, 2 mM CHAPS, 2 mM EDTA, 1 mM DTT) in the presence of the test compound(s) for 2-4 hours at room temperature. Data was collected using an LJL Analyst with readings at 615 nm and 665 nm.

EXAMPLE 54

FXR Co-Transfection Assay

The basic co-transfection protocol for measuring FXR activity is as follows. CV-1 African Green Monkey Kidney cells are plated 24 hours before transfection to achieve approximately 70-80 percent confluency. Cells are transfected with CMX-hFXR, CMX-RXRα, Luc12 reporter (ECREx7-Tk-Luciferase), and a CMX-β-Galactosidase expression vector. The transfection reagent used is DOTAP. Cells are incubated with the DOTAP/DNA mixture for 5 hours after which the cells are harvested and plated onto either 96 well or 384 well plates containing the appropriate concentration of test compound. The assay is allowed to continue for an additional 18-20 hours, after which the cells are lysed, and the luciferase activity is measured on a standard plate reader.

Results of Examples 53 and 54

Both the FXR/ECREx7 co-transfection assay (Example 54) and the TR-FRET assay (Example 53) can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control (chenodeoxycholic acid, CDCA) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. The curve for the data is generated by using the equation:

Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

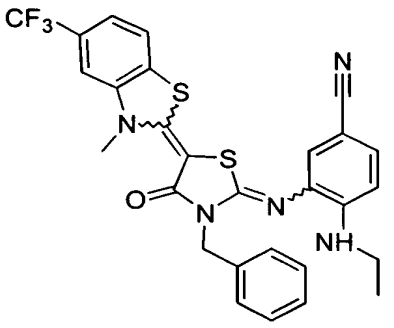
The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by chenodeoxycholic acid that is measured individually in each dose response experiment.

For the antagonist assay, 40 μM CDCA is added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of 40 μM CDCA. In this example 100% inhibition would indicate that the activity of 40 μM CDCA has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays (EC_{50} or IC_{50} less than 10 μM). Most showed activity at below 1 μM. Some showed activity below 100 nM. For example, 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile (Example 32) shows an EC_{50} of about 0.010 μM and a % efficacy of about 150% in the co-transfection assay; and 3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile (Example 52) shows an EC_{50} of about 0.056 μM and a % efficacy of about 32% in the co-transfection assay; and an IC_{50} of about 0.042 μM and a % inhibition of about 48% in a FRET assay.

EXAMPLE 55

Preparation of 3-{3-benzyl-5-[3-methyl-5-(trifluoromethyl)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)b nzonitril



To a suspension of 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride (4.58 g, 20 mmol) in $CHCl_3$ (50 mL) was added saturated aqueous Na_2CO_3 (50 mL). To this stirred biphasic mixture was added $CSCl_2$ (1.57 mL, 20 mmol) dropwise. After the addition was complete, the mixture was stirred for 72 h at 20 °C. The organic layer was separated and the aqueous layer was extracted by $CHCl_3$ (3x20 mL). The combined organic layer was washed by water and dried over $MgSO_4$. Evaporation of solvent gave 2-mercapto-5-(trifluoromethyl)benzothiazole (1.27 g), which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$): δ 7.23 (1H, d), 6.94 (1H, s), 6.81 (1H, d), 4.53 (s, 1 H).

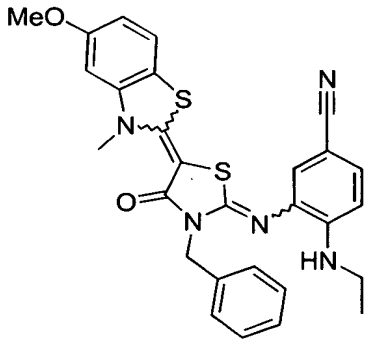
To a suspension of the above compound in anisole (10 mL) was added methyl tosylate (MeOTs) (2.5 mL, 2 equiv) and the suspension was heated to 130 °C for 3 h. After cooling to 20 °C, acetonitrile and 3-benzylrhodanine were added. To this suspension was added TEA (3 mL, 4 equiv) dropwise, yellow precipitate appeared immediately. The suspension was stirred for 5 h at 20 °C. The yellow solid was collected by filtration and washed by acetonitrile and dried under high vacuum to give the product (360 mg).

To a suspension of the above compound in DMF (4 mL) was added MeOTs (0.45 mL, 3 equiv) and the resulted suspension was heated to 130 °C for 5 h. After cooling to 20 °C, acetone was added to precipitate the product. Solid was collected by filtration and washed by acetone and dried under high vacuum to afford the tosylate salt (110 mg).

A mixture of the above compound (56 mg, 0.1 mmol), 3-amino-4-(ethylamino)benzonitrile (16 mg, 0.1 mmol) and TEA (28 µL, 0.2 mmol) was shaken at 60 °C overnight. Evaporation of solvent gave a crude, which was purified by trituration with MeOH to afford the title compound (27 mg). ^{1}H-NMR indicated one isomer. ^{1}H-NMR ($CDCl_3$): δ 7.61 (1H, d), 7.44 (2H, m), 7.35 (2H, m), 7.27-7.31 (4H, m), 7.18 (1H), 6.5 (1H), 5.19 (2H, s), 4.19 (1H, t), 3.84 (3H, s), 3.01 (2H, m), 1.03 (3H, t); MS (ESI): 566 (MH^+).

EXAMPLE 56

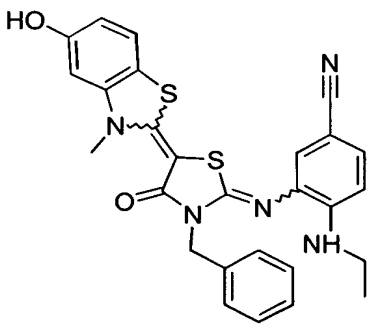
Preparation of 3-[3-benzyl-5-(3-methyl-5-methoxy-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 55 by starting from 2-mercapto-5-methoxy-benzothiazole. ^{1}H-NMR indicated one isomer. ^{1}H-NMR (DMSO-d_3): δ 7.47 (1H, d), 7.13-7.21 (5H, m), 6.98 (1H, d), 6.86 (1H, d), 6.67 (1H, dd), 6.46 (1H, d), 4.96 (2H, s), 4.81(1H, m), 3.66 (3H, s), 3.65 (3H, s), 2.89 (2H, m), 0.83 (3H, t); MS (ESI): 528 (MH^+).

EXAMPLE 57

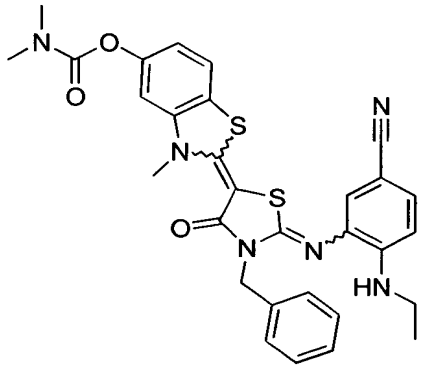
Preparation of 3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile



To a suspension of the product of Example 56 (1.06 g, 2 mmol) in DCM (10 mL) was added BBr_3 (1.0 M in DCM, 2 mL) dropwise at –78 °C. It was warmed to 20 °C slowly and the suspension was stirred for 72 h at 20 °C under N_2. MeOH was added to decompose BBr_3 at 0 °C. Solvent was removed to give a crude, which was purified by chromatography on silica gel eluting with MeOH-DCM (2.5 :97.5) to afford the title compound (0.6 g). ^{1}H-NMR indicated one isomer. ^{1}H-NMR (DMSO-d_6): δ 9.66 (1H, s), 7.35 (1H, d), 7.13-7.24 (5H, m), 6.99 (1H, d), 6.60 (1H, d), 6.53 (1H, dd), 6.46 (1H, d), 4.96 (2H, s), 4.82(1H, t), 3.58 (3H, s), 2.89 (2H, m), 0.84 (3H, t); MS (ESI): 514 (MH^+).

EXAMPLE 58

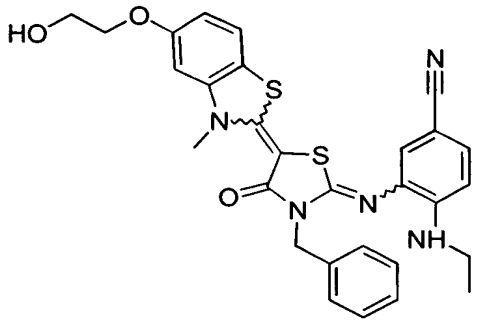
Preparation of Dimethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester



To a suspension of the product of Example 57 in $CHCl_3$ was added TEA (84 µL, 0.6 mmol) and dimethylcarbamoyl chloride (56 µL, 0.6 mmol). The resulting suspension was heated to 65 °C overnight with shaking. Solvent was removed under vacuum to give a crude, which was purified by chromatography on silica gel, eluting by MeOH-DCM (5:95) to afford the title compound (38.6 mg). ^{1}H-NMR indicated one isomer. ^{1}H-NMR (DMSO-d_6): δ 97.73 (1H, d), 7.28-7.39 (7H, m), 7.14 (1H, d), 6.97 (1H, dd), 6.63 (1H, dd), 5.12 (2H, s), 4.98(1H, t), 3.78 (3H, s), 3.05 (6H, m), 2.91 (3H, s), 0.99 (3H, t); MS (ESI): 585 (MH^+).

EXAMPLE 59

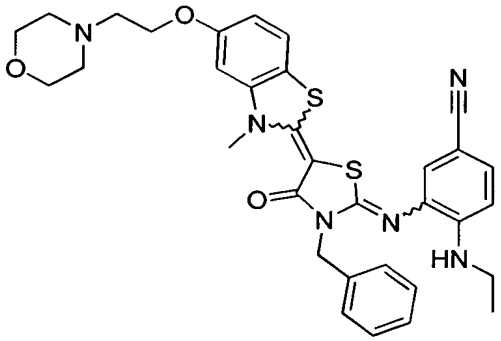
Preparation of 3-{3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



To a solution of the product of Example 57 in DMF were added K_2CO_3 and 3-bromoethanol and the resulting suspension was heated to 75 °C with stirring under nitrogen for 72 h. Solid was removed by filtration and washed by DMF. Evaporation of solvent gave a crude, which was purified by chromatography on silica gel eluting with MeOH-DCM (5:95) to afford the title compound (0.58 g). ^{1}H-NMR indicated one isomer. ^{1}H-NMR (DMSO-d_6): δ 7.62 (1H, d), 7.29-7.39 (5H, m), 7.14 (1H, d), 7.02 (1H, d), 6.84 (1H, dd), 5.75 (1H, d), 5.11 (2H, s), 4.97 (1H, t), 4.87(1H, t), 4.05 (2H, t), 3.80 (3H, s), 3.71 (2H, m), 3.05 (2H, m), 0.99 (3H, t); MS (ESI): 558 (MH^+).

EXAMPLE 60

Preparation of 3-{3-benzyl-5-[3-methyl-(2-morpholin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile

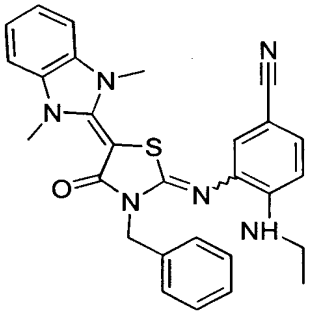


To a suspension of the product of Example 59 (56 mg, 0.1 mmol) in anhydrous DCM (2 mL) was added triflic anhydride (Tf_2O) at -10 °C under

nitrogen. The suspension was stirred for 1 h at -10 °C. Morpholine (44 µL, 0.5 mmol) was added and the reaction mixture was stirred overnight at 20 °C. Evaporation of solvent gave a crude, which was purified by chromatography on silica gel eluting with MeOH-DCM to give the title compound (18 mg). ^{1}H-NMR indicated one isomer. ^{1}H-NMR ($CDCl_3$): δ 7.44 (2H, m), 7.39 (1H, d), 7.32-7.36 (2H, m), 7.27-7.30 (2H, m), 7.20 (1H, d), 6.78 (1H, dd), 6.67 (1H, d), 6.49 (1H, d), 5.17 (2H, s), 4.22 (1H, t), 4.15 (2H, t), 3.78 (3H, s), 3.75 (4H, m), 3.01 (2 H, m), 2.83 (2H, t), 2.59 (2 H, t), 1.02 (3 H, t); MS (ESI): 627 (MH^+).

EXAMPLE 61

3-[3-benzyl-5-(1,3-dimethyl-1,3-dihydrobenzoimidazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile



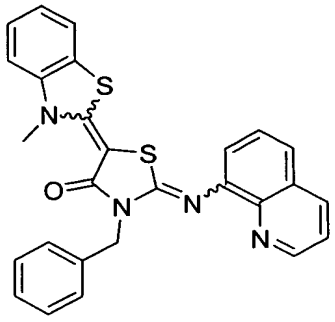
To a suspension of 2-mercaptobenzimidazole (15.02 g, 100 mmol) in aqueous $NaHCO_3$ (25.2 g, 300 mmol in 40 mL of H_2O) was added Me_2SO_4 (47.4 mL, 500 mmol) dropwise at 20 °C. A clear solution was obtained. The solution was stirred for 17 h at 20 °C. NaI (3.2 g, 200 mmol) was added. After the solution was cooled in an ice-water bath, yellowish precipitate appeared. Solid was collected by filtration and washed by cold water and ether. Drying under high vacuum afforded the iodide salt (6.5 g).

To a solution of the above salt (66 mg, 0.2 mmol) and 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzonitrile (70 mg, 0.2 mmol) in DMF was added DBU (62 mL, 2 equiv) and the solution was heated to 100 °C for 48 h. Evaporation of solvent under high vacuum gave a crude, which was purified by chromatography on silica gel eluting with EtOAc-hexane (1:1) to give the title compound (3.6 mg). ^{1}H-NMR indicated one isomer. ^{1}H-NMR

($CDCl_3$): δ 7.46 (2H, m), 7.22-7.36 (8H, m), 6.46 (1H,d), 5.17 (2H, s), 4.44 (1H, t), 3.79 (3H, s), 3.01 (2 H, m), 0.88 (3 H, t); MS (ESI): 495 (MH^+).

EXAMPLE 62

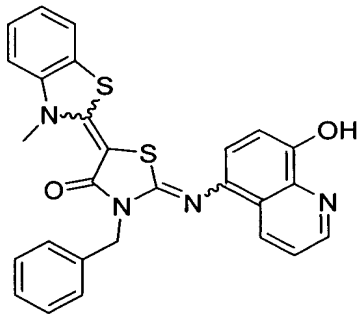
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylid ne)-2-(quinolin-8-ylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 8-aminoquinoline. MS(ESI): 481 (MH^+).

EXAMPLE 63

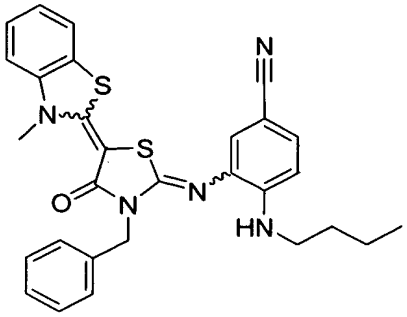
Preparation of 3-benzyl-2-(8-hydroxyquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoquinolin-8-ol. MS(ESI): 497 (MH^+).

EXAMPLE 64

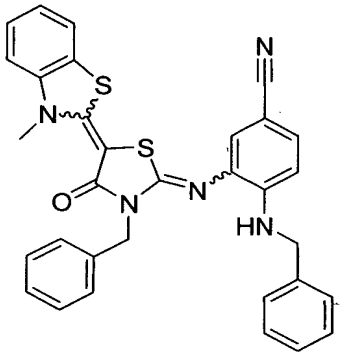
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-yliden amino]-4-butylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with butylamine. MS(ESI): 526 (MH^+).

EXAMPLE 65

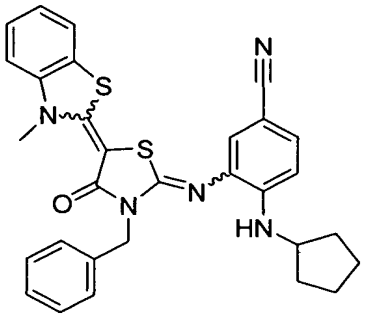
Preparation of 4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with benzylamine. MS(ESI): 560 (MH^+).

EXAMPLE 66

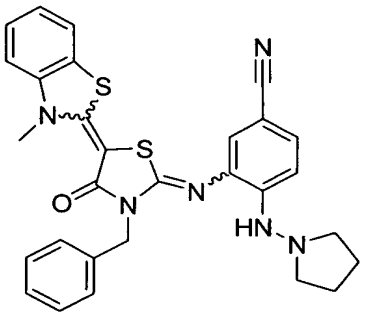
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyclopentylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with cyclopentylamine. MS(ESI): 538 (MH^+).

EXAMPLE 67

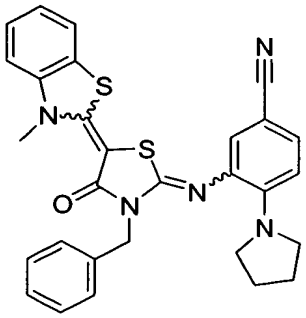
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(pyrrolidin-1-ylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 1-aminopyrrolidine. MS(ESI): 539 (MH^+).

EXAMPLE 68

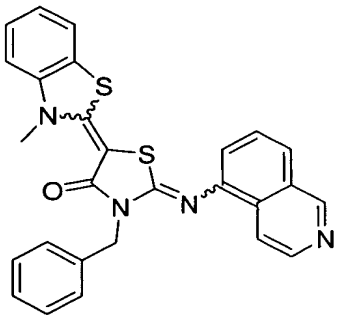
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-pyrrolidin-1-ylbenzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with pyrrolidine. MS(ESI): 524 (MH^+).

EXAMPLE 69

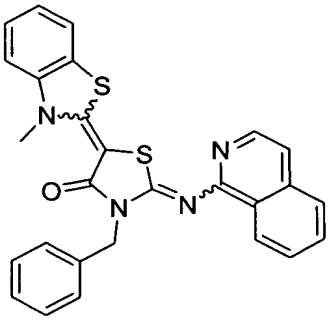
Preparation of 3-benzyl-2-(isoquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoisoquinoline. MS(ESI): 481 (MH^+).

EXAMPLE 70

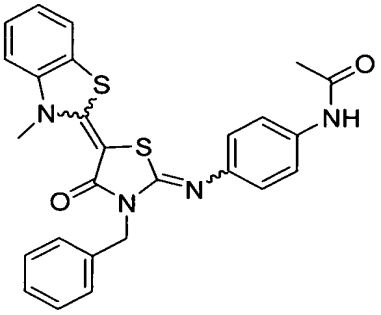
Preparation of 3-benzyl-2-(isoquinolin-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-aminoisoquinoline. MS(ESI): 481 (MH^+).

EXAMPLE 71

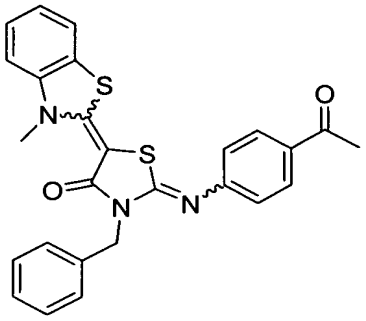
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminoacetanilide. MS(ESI): 487 (MH^+).

EXAMPLE 72

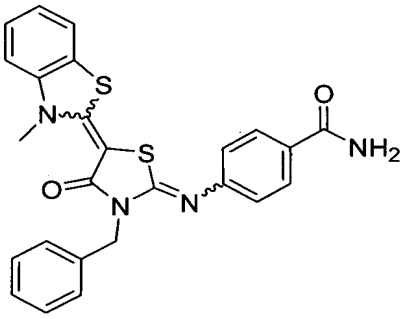
Preparation of 2-(4-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminoacetophenone. MS(ESI): 482 (MH^+).

EXAMPLE 73

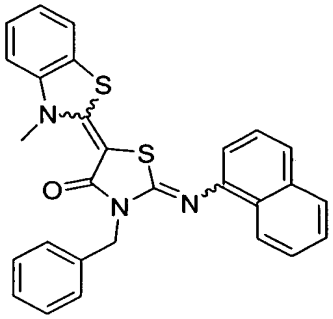
Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminobenzamide. MS(ESI): 473 (MH^+).

EXAMPLE 74

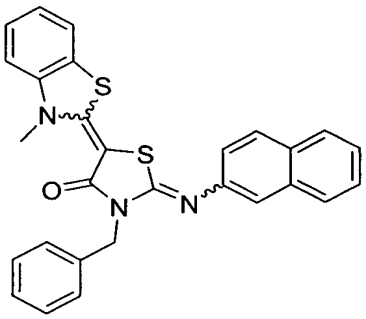
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-1-ylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-naphthylamine. MS(ESI): 480 (MH^+).

EXAMPLE 75

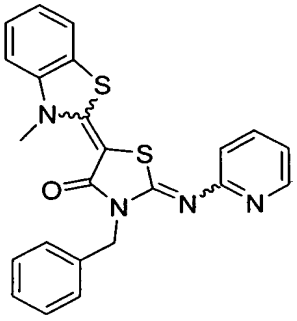
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-2-ylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 2-naphthylamine. MS(ESI): 480 (MH^+).

EXAMPLE 76

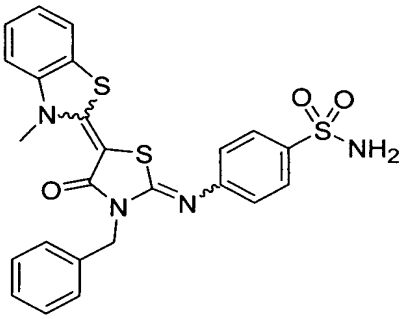
Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-2-ylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-aminopyridine. MS(ESI): 431 (MH^+).

EXAMPLE 77

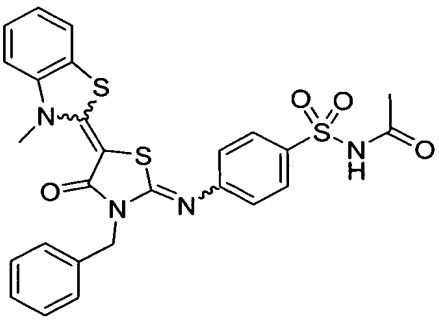
Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminobenzenesulfonamide. MS(ESI): 509 (MH^+).

EXAMPLE 78

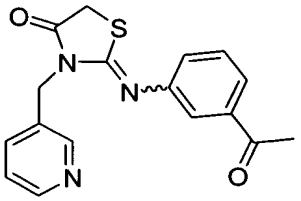
Preparation of N-acetyl-4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with N-acetyl-4-aminobenzenesulfonamide. MS(ESI): 551 (MH^+).

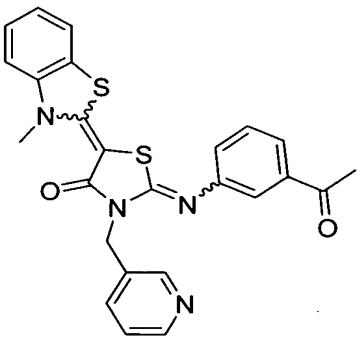
EXAMPLE 79

A. Preparation of 2-(3-acetylphenylimino)-3-pyridin-3-ylmethylthiazolidin-4-one



The title compound was prepared from 3-picolyl isothiocyanate hydrobromide and 3'-aminoacetophenone in a manner similar to Example 52. ^{1}H-NMR ($CDCl_3$): δ 8.80 (1H, d), 8.58 (1H, dd), 7.85 (1H, m), 7.74 (1H, m), 7.54 (1H, m), 7.45 (1H, m), 7.29 (1H, m), 7.15 (1H, m), 5.05 (2H, s), 3.86 (2H, s), 2.60 (3H, s).

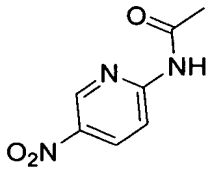
B. Preparation of 2-(3-acetylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one



The title compound was prepared from intermediate 2-(3-acetylphenylimino)-3-pyridin-3-ylmethylthiazolidin-4-one and 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate as described in Example 45. ^{1}H-NMR ($CDCl_3$): δ 8.87 (1H, d), 8.56 (1H, dd), 7.93 (1H, m), 7.74 (1H, m), 7.60 (1H, m), 7.53 (1H, d), 7.46 (1H, m), 7.27-7.38 (2H, m), 7.17-7.23 (2H, m), 7.05 (1H, d), 5.18 (2H, s), 3.74 (3H, s), 2.62 (3H, s); MS(ESI): 473 (MH^+).

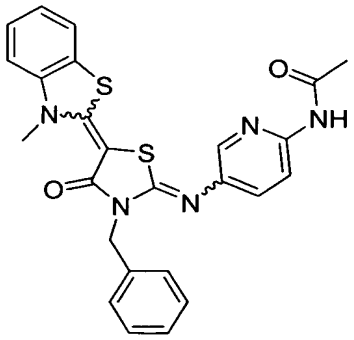
EXAMPLE 80

A. Preparation of N-(5-nitropyridin-2-yl)acetamide



To a hot solution of 2-amino-5-nitropyridine (1.4 g, 10 mmol) in acetic anhydride (5 mL) at 100°C was added conc. H_2SO_4 (0.1 mL). The resulting mixture was heated at 130°C for 2h, cooled and partitioned between EtOAc (200 mL) and water (100 mL). The layers were separated and the aqueous layer was washed once with EtOAc (100 mL). The combined organic layers were washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and then brine (50 mL); dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford N-(5-nitropyridin-2-yl)acetamide (1.8 g, 98%), which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 9.14 (1H, d), 8.50 (1H, dd), 8.40 (1H, d), 8.23 (1H, br s), 2.29 (3H, s).

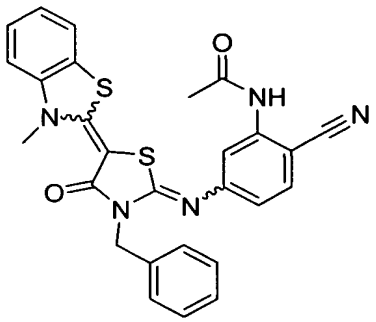
B. Preparation of N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]pyridin-2-yl}acetamide



In a manner similar to Example 30, intermediate N-(5-nitropyridin-2-yl)acetamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR (DMSO-d_6): δ 10.45 (1H, s), 8.07 (1H, d), 7.97 (1H, d), 7.75 (1H, d), 7.33-7.46 (7H, m), 7.29 (1H, m), 7.22 (1H, m), 5.06 (2H, s), 3.79 (3H, s), 2.09 (3H, s); MS(ESI): 488 (MH^+).

EXAMPLE 81

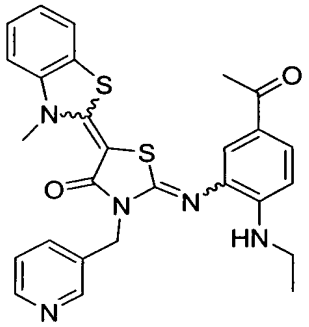
Preparation of N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5'-amino-2'-cyanoacetanilide. MS(ESI): 512 (MH^+).

EXAMPLE 82

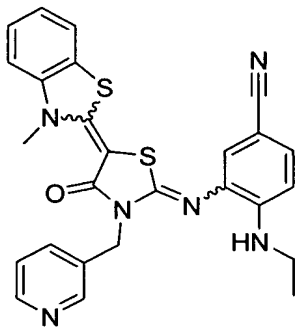
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 79 by replacing 3'-aminoacetophenone with 3'-amino-4'-(ethylamino)acetophenone. MS(ESI): 516 (MH^+). Recrystallization of the product from hot ethanol afforded crystals suitable for single-crystal X-ray diffraction. Structural analysis showed that the E-isomer had been obtained.

EXAMPLE 83

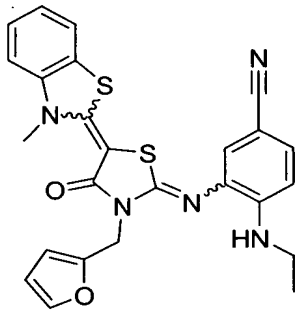
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 79 by replacing 3'-aminoacetophenone with 3-amino-4-(ethylamino)benzonitrile. MS(ESI): 499 (MH^+).

EXAMPLE 84

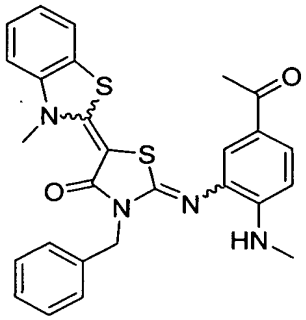
Preparation of 4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. MS(ESI): 488 (MH^+).

EXAMPLE 85

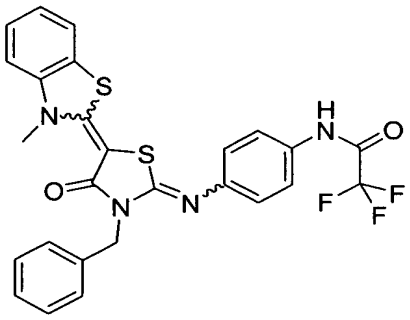
Preparation of 2-(5-acetyl-2-methylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 31 by replacing 4-fluoro-3-nitrobenzonitrile with 4'-chloro-3'-nitroacetophenone. MS(ESI): 501 (MH^+).

EXAMPLE 86

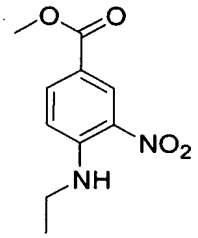
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2,2,2-trifluoroacetamide



The product of Example 4 was treated with trifluoroacetic anhydride in anhydrous DCM. After 1h the product mixture was diluted with EtOAc, washed with water and satd aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.81 (1H, br s), 7.53-7.59 (4H, m), 7.49 (1H, d), 7.27-7.36 (4H, m), 7.17 (1H, m), 7.01-7.06 (3H, m), 5.15 (2H, s), 3.73 (3H, s); MS(ESI): 541 (MH^+).

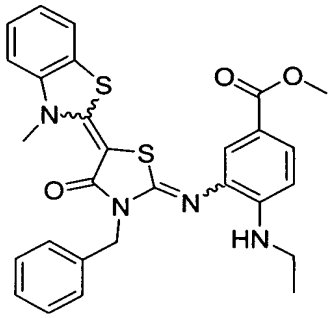
EXAMPLE 87

A. Preparation of 4-ethylamino-3-nitrobenzoic acid methyl ester



In a manner similar to Example 31, 4-fluoro-3-nitrobenzoic acid was treated with ethylamine to give 4-ethylamino-3-nitrobenzoic acid, which was then esterified with anhydrous hydrogen chloride in methanol to give the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.89 (1H, d), 8.28 (1H, br s), 8.06 (1H, dd), 6.87 (1H, d), 3.90 (3H, s), 3.42 (2H, m), 1.40 (3H, t).

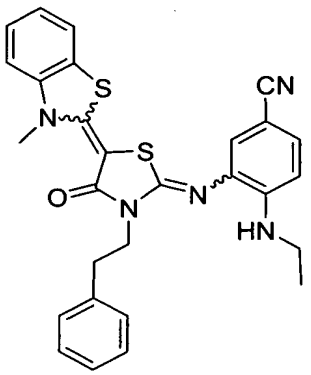
B. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid methyl ester



In a manner similar to Example 30, intermediate 4-ethylamino-3-nitrobenzoic acid methyl ester was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.73 (1H, dd), 7.65 (1H, d), 7.52 (1H, dd), 7.45-7.49 (2H, m), 7.27-7.38 (4H, m), 7.18 (1H, m), 7.06 (1H, d), 6.52 (1H, d), 5.19 (2H, s), 4.14 (1H, br t), 3.85 (3H, s), 3.78 (3H, s), 3.04 (2H, m), 1.04 (3H, t); MS(ESI): 531 (MH^+).

EXAMPLE 88

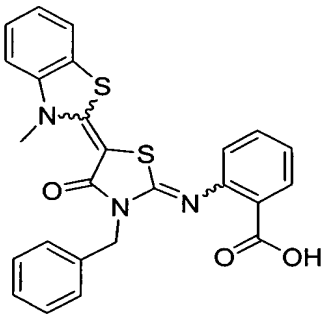
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylid ne)-4-oxo-3-phenethylthiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with phenethyl isothiocyanate. MS(ESI): 512 (MH^+).

EXAMPLE 89

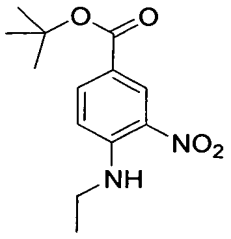
Preparation of 2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with anthranilic acid. MS(ESI): 474 (MH^+).

EXAMPLE 90

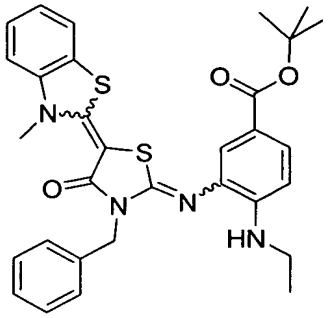
A. Preparation of 4-ethylamino-3-nitrobenzoic acid *tert*-butyl ester



4-Chloro-3-nitrobenzoic acid *tert*-butyl ester (3.0 g, 11.6 mmol), prepared according to a published procedure [WO 9707101], was cautiously

added to a solution of 2.0 M $EtNH_2$/THF (20 mL, 40 mmol) and TEA (2.0 mL, 14 mmol) in anhydrous THF (30 mL). The resulting mixture was heated at 65°C for 3h, cooled, concentrated under reduced pressure, diluted with DCM (200 mL), washed with water (2 x 100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give the title compound (3.1 g, 99%) as a yellow solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.80 (1H, d), 8.24 (1H, br s), 8.02 (1H, dd), 6.84 (1H, d), 3.41 (2H, m), 1.59 (9H, s), 1.40 (3H, t).

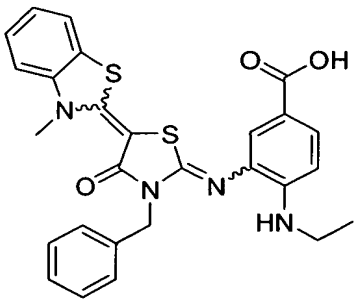
B. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid *tert*-butyl ester



In a manner similar to Example 30, intermediate 4-ethylamino-3-nitrobenzoic acid *tert*-butyl ester was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.69 (1H, dd), 7.61 (1H, d), 7.52 (1H, dd), 7.45-7.49 (2H, m), 7.27-7.37 (4H, m), 7.18 (1H, m), 7.06 (1H, d), 6.51 (1H, d), 5.19 (2H, s), 4.11 (1H, br t), 3.79 (3H, s), 3.04 (2H, m), 1.57 (9H, s), 1.04 (3H, t); MS(ESI): 573 (MH^+).

EXAMPLE 91

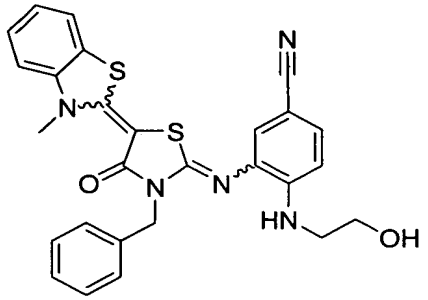
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid



The product of Example 90 was treated with 55% TFA/DCM for 1h, concentrated under reduced pressure, diluted with DCM, concentrated once again, diluted with DCM, allowed to stand over solid $NaHCO_3$, filtered and concentrated to afford the title product. MS(ESI): 517 (MH^+).

EXAMPLE 92

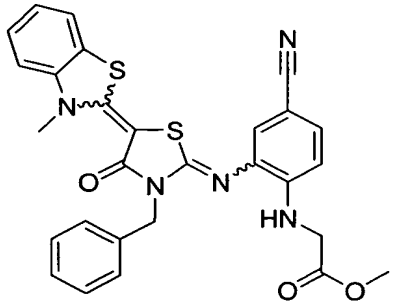
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-hydroxyethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 2-aminoethanol. ^{1}H-NMR ($CDCl_3$): δ 7.52 (1H, d), 7.42-7.49 (4H, m), 7.27-7.37 (4H, m), 7.19 (1H, m), 7.05 (1H, d), 6.57 (1H, d), 5.94 (1H, br t), 5.19 (2H, s), 3.76 (3H, s), 3.48 (2H, m), 3.03 (2H, q), 1.23 (3H, t), 1.04 (3H, t); MS(ESI): 514 (MH^+).

EXAMPLE 93

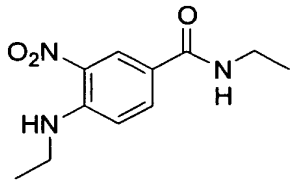
Preparation of {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid methyl ester



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with glycine methyl ester. MS(ESI): 542 (MH^+).

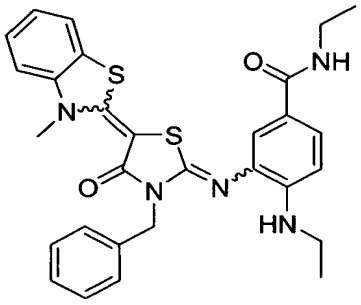
EXAMPLE 94

A. Preparation of N-ethyl-4-ethylamino-3-nitrobenzamide



In a manner similar to Example 31, the title compound was prepared from 4-fluoro-3-nitrobenzoic acid (as a mixed anhydride) and ethylamine. ^{1}H-NMR ($CDCl_3$): δ 8.52 (1H, d), 8.21 (1H, br s), 7.98 (1H, dd), 6.90 (1H, d), 6.06 (1H, br s), 3.46-3.57 (2H, m), 3.38-3.45 (2H, m), 1.40 (3H, t), 1.27 (3H, t).

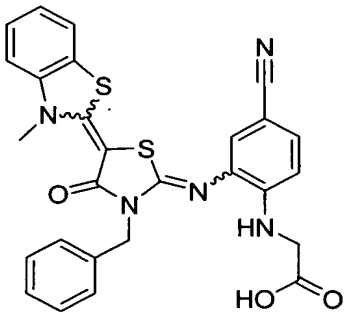
B. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-4-ethylaminobenzamide



In a manner similar to Example 30, intermediate N-ethyl-4-ethylamino-3-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 544 (MH^+).

EXAMPLE 95

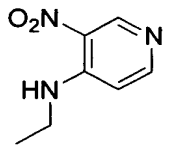
Preparation of {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid



The product of Example 93 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 528 (MH^+).

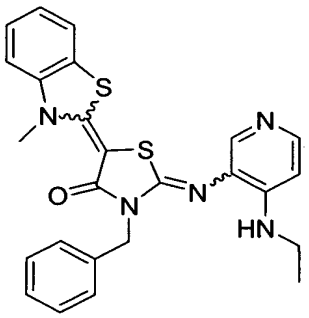
EXAMPLE 96

A. Preparation of 4-ethylamino-3-nitropyridine



In a manner similar to example 31, the title compound was prepared from 4-chloro-3-nitropyridine, prepared according to published procedure [*J. Med. Chem.* **1996**, *39*, 487-493], and ethylamine. ^{1}H-NMR ($CDCl_3$): δ 9.22 (1H, s), 8.30 (1H, d), 8.10 (1H, br s), 6.71 (1H, d), 3.40 (2H, m), 1.39 (3H, t).

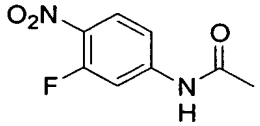
B. Preparation of 3-benzyl-2-(4-ethylaminopyridin-3-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



In a manner similar to Example 30, intermediate 4-ethylamino-3-nitropyridine was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.04-8.09 (2H, m), 7.53 (1H, d), 7.44-7.48 (2H, m), 7.27-7.38 (4H, m), 7.19 (1H, m), 7.07 (1H, d), 6.42 (1H, d), 5.19 (2H, s), 4.12 (1H ,br t), 3.79 (3H, s), 3.02 (2H, m), 1.05 (3H, t); MS(ESI): 474 (MH^+).

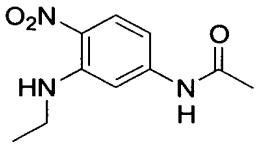
EXAMPLE 97

A. Preparation of 3'-fluoro-4'-nitroacetanilide



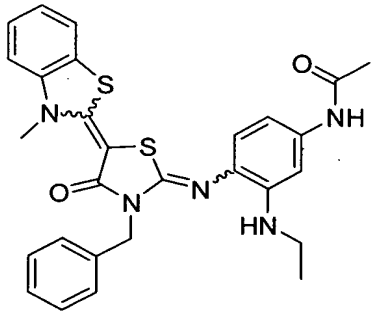
Added 3'-fluoroacetanilide (3.06 g, 20 mmol) cautiously to concentrated sulfuric acid (6 mL) at 5°C. To the resulting solution, added fuming nitric acid (1.05 mL, 25 mmol) dropwise while maintaining temperature at 5-10°C. After 30 min, added ice (50 g), later diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude product (4.0 g) as a mixture of isomers (1:1.4 ratio of 4'-nitro/2'-nitro). The desired isomer, 3'-flouro-4'-nitroacetanilide, was isolated by flash chromatography (DCM – 5% MeOH/DCM) in low yield (1.2 g, 30%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.08 (1H, app t), 7.82 (1H, dd), 7.41 (1H, br s), 7.21 (1H, m), 2.25 (3H, s).

B. Preparation of 3'-ethylamino-4'-nitroacetanilide



In a manner similar to Example 31, the title compound was prepared from 3'-fluoro-4'-nitroacetanilide and ethylamine. ^{1}H-NMR ($CDCl_3$): δ 8.17 (1H, br s), 8.13 (1H, d), 7.57 (1H, br d), 7.33 (1H, br s), 6.38 (1H, dd), 3.36 (2H, m), 2.22 (3H, s), 1.37 (3H, t).

C. Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-3-ethylaminophenyl}acetamide

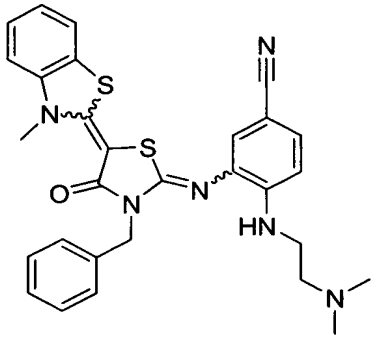


In a manner similar to Example 30, intermediate 3'-ethylamino-4'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.45-7.53 (3H, m), 7.27-7.37 (4H, m), 7.17 (1H, m), 7.03-7.09 (2H, m), 6.91 (1H, d), 6.83

(1H, br d), 6.75 (1H, br s), 5.18 (2H, s), 3.78 (3H, s), 2.99 (2H, m), 2.15 (3H, s), 1.03 (3H, t); MS(ESI): 530 (MH^+).

EXAMPLE 98

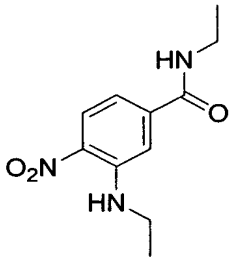
Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-dimethylaminoethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with N,N-dimethylethylenediamine. MS(ESI): 541 (MH^+).

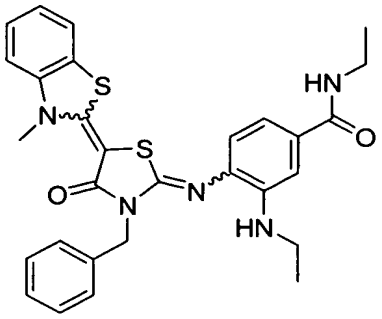
EXAMPLE 99

A. Preparation of N-ethyl-3-ethylamino-4-nitrobenzamide



To a chilled solution (10°C) of 3-fluoro-4-nitrobenzoyl chloride (1.0 g, 4.9 mmol) in anhydrous THF (30 mL) added dropwise 2.0 M solution of ethylamine in THF (10 mL, 20 mmol). After stirring 16h at 25°C, combine with saturated $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with 1 N NaOH (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the title compound (0.66 g, 57%) as an orange-yellow solid that was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.20 (1H, d), 7.98 (1H, br s), 7.36 (1H, d), 6.81 (1H, dd), 6.13 (1H, br s), 3.51 (2H, m), 3.42 (2H, m), 1.39 (3H, t), 1.27 (3H, t).

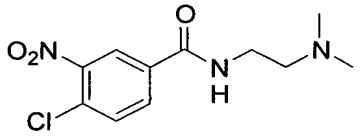
B. Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-3-ethylaminobenzamide



In a manner similar to Example 30, intermediate N-ethyl-3-ethylamino-4-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.46-7.54 (3H, m), 7.27-7.38 (4H, m), 7.19 (1H, m), 6.96-7.08 (4H, m), 6.04 (1H, br t), 5.19 (2H, s), 3.76 (3H, s), 3.49 (2H, m), 3.06 (2H, q), 1.25 (3H, t), 1.05 (3H, t); MS(ESI): 544 (MH^+).

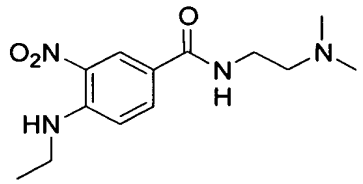
EXAMPLE 100

A. Preparation of 4-chloro-N-(2-dimethylaminoethyl)-3-nitrobenzamide



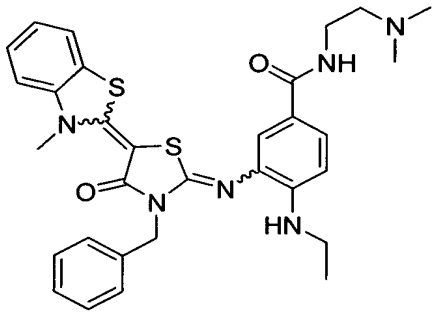
To a chilled solution (-10°C) of 4-chloro-3-nitrobenzoyl chloride (0.92 g, 4.2 mmol) in anhydrous THF (20 mL) added dropwise a solution of N,N-dimethylethylenediamine (0.44 mL, 4.0 mmol) in THF (20 mL). After stirring 30 min combined with a 1:1 mixture of ice and saturated $NaHCO_3$ (50 mL) and then extracted with EtOAc (3 x 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4,concentrated and chromatographed (silica gel, MeOH/DCM, 3:22) to yield the title compound (0.40 g, 37%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.28 (1H, d), 7.96 (1H, dd), 7.63 (1H, d), 6.98 (1H, br s), 3.54 (2H, m), 2.56 (2H, t), 2.30 (6H, s)

B. Preparation of N-(2-dimethylaminoethyl)-4-ethylamino-3-nitr benzamide



To 2.0 M solution of ethylamine in THF (8 mL, 16 mmol) slowly added 4-chloro-N-(2-dimethylaminoethyl)-3-nitrobenzamide (0.40 g, 1.5 mmol). After heating at 65°C for 16h, the reaction mixture was cooled, concentrated and chromatographed (silica gel, MeOH/DCM, 3:22) to afford the title compound (0.30 g, 73%) as a yellow solid. ^{1}H-NMR (CD_3OD): δ 8.75 (1H, d), 8.32 (1H, br s), 7.98 (1H, dd), 7.08 (1H, d), 3.58-3.64 (3H, m), 3.43-3.51 (2H, m), 2.94 (2H, br t), 2.62 (6H, s), 1.35 (3H, t).

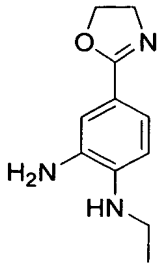
C. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-(2-dimethylaminoethyl)-4-ethylaminobenzamide



In a manner similar to Example 30, intermediate N-(2-dimethylaminoethyl)-4-ethylamino-3-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.54 (5H, m), 7.28-7.38 (4H, m), 7.18 (1H, m), 7.04 (1H, d), 6.89 (1H, br s), 6.52 (1H, d), 5.19 (2H, s), 3.99 (1H, br t), 3.76 (3H, s), 3.59 (2H, m), 3.02 (2H, m), 2.68 (2H, br s), 2.40 (6H, s), 1.03 (3H, t); MS(ESI): 587 (MH^+).

EXAMPLE 101

A. Preparation of 4-(4,5-dihydrooxazol-2-yl)-N^1-ethylbenzene-1,2-diamine



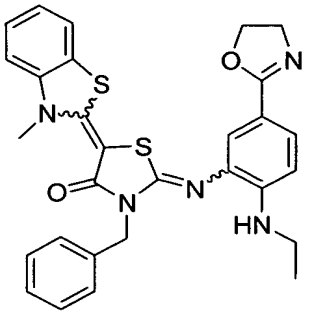
To a chilled solution (-10°C) of 4-chloro-3-nitrobenzoyl chloride (1.85 g, 8.4 mmol) in anhydrous THF (60 mL) was added dropwise a solution of ethanolamine (0.48 mL, 8.0 mmol) in THF (20 mL) followed by TEA (1.1 mL, 8.0 mmol). After stirring 1h while temperature was maintained at -10°C, the solution was combined with a 1:1 mixture of ice and saturated $NaHCO_3$ (100 mL) and then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 4-chloro-*N*-(2-hydroxyethyl)-3-nitrobenzamide (1.74 g, 89%) as a white solid, which was used without purification. TLC (3:22 MeOH/DCM R_f 0.36).

To a solution of intermediate 4-chloro-*N*-(2-hydroxyethyl)-3-nitrobenzamide (0.40 g, 1.6 mmol) in anhydrous DCM (20 mL) added dropwise thionyl chloride (0.29 mL, 4.0 mmol). After stirring 2h the reaction mixture was diluted with chloroform and concentrated. The resulting yellow oil was diluted cautiously with 2.0 M solution of ethylamine in THF (10 mL, 20 mmol) and heated in a sealed tube at 65°C. After 2h the reaction mixture was cooled, concentrated and diluted with THF (20 mL). This solution was combined with an aqueous solution of 20% KOH (5 mL) and tetrabutylammonium bromide (20 mg). After stirring rapidly 2h the mixture was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, concentrated and chromatographed (silica gel, MeOH/DCM, 1:19) to yield [4-(4,5-dihydrooxazol-2-yl)-2-nitrophenyl]ethylamine (0.17 g, 45%) as a yellow solid. TLC (1:19 MeOH/DCM R_f 0.56).

To a solution of this oxazoline intermediate (71 mg, 0.30 mmol) in ethanol (2 mL) was added zinc dust (0.20 g) and HOAc (0.20 mL). Observed

initial exotherm and continued stirring 30min. The reaction mixture was diluted with Et_2O (20 mL), filtered, combined cautiously with 15% NH_4OH (10 mL), and extracted again with Et_2O. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the title compound (60 mg, 97%) as an off-white solid, which was used without purification. ^{1}H-NMR ($CDCl_3$): δ 7.45 (1H, dd), 7.35 (1H, d), 6.60 (1H, d), 4.38 (2H, t), 4.01 (2H, t), 3.69 (1H, br s), 3.26 (2H, br s), 3.21 (2H, m), 1.32 (3H, t); TLC (1:19 MeOH/DCM R_f 0.12).

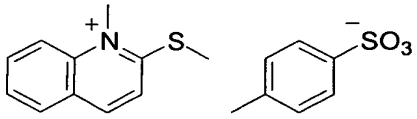
B. Preparation of 3-benzyl-2-[5-(4,5-dihydrooxazol-2-yl)-2-ethylamino-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to Example 1 by replacing aniline with intermediate 4-(4,5-dihydrooxazol-2-yl)-N^1-ethylbenzene-1,2-diamine. ^{1}H-NMR ($CDCl_3$): δ 7.64 (1H, d), 7.55 (1H, d), 7.52 (1H, d), 7.45-7.49 (2H, m), 7.27-7.37 (4H, m), 7.18 (1H, m), 7.04 (1H, d), 6.55 (1H, d), 5.19 (2H, s), 4.38 (2H, t), 4.02 (2H, t), 3.77 (3H, s), 3.04 (2H, m), 1.05 (3H, s); MS(ESI): 542 (MH^+).

EXAMPLE 102

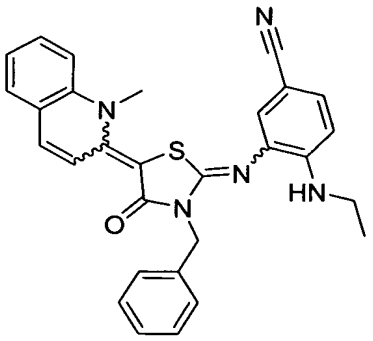
A. Preparation of 1-methyl-2-methylthioquinolinium *p*-toluenesulfonate



A mixture of 1-methylquinolin-2-thione (175 mg, 1.0 mmol) and methyl *p*-toluenesulfonate (186 mg, 1.0 mmol) was heated at 130°C. After 30 min the resulting solid was cooled, crushed, triturated with Et_2O (4 x 1 mL) and dried under high vacuum to give the title compound (0.35 g, 97%) as a white solid. ^{1}H-NMR (DMSO-d_6): δ 8.96 (1H, d), 8.46 (1H, d), 8.35 (1H, dd), 8.16

(1H, m), 8.08 (1H, d), 7.91 (1H, m), 7.47 (2H, d), 7.10 (2H, d), 4.40 (3H, s), 3.02 (3H, s), 2.28 (3H, s)

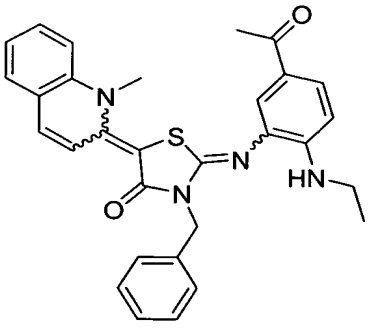
B. Preparation of 3-[3-b nzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



In a manner similar to Example 45, intermediate 1-methyl-2-methylthioquinolinium *p*-toluenesulfonate was condensed with 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.41-7.58 (4H, m), 7.20-7.38 (9H, m), 6.49 (1H, d), 5.16 (2H, s), 3.79 (3, br s), 3.01 (2H, q), 1.02 (3H, t); MS(ESI): 492 (MH^+).

EXAMPLE 103

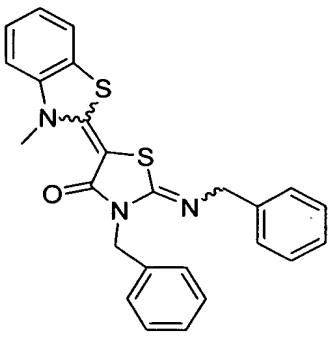
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)thiazolidin-4-one



In a manner similar to Example 102, 1-methyl-2-methylthioquinolinium *p*-toluenesulfonate was condensed with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.66-7.71 (2H, m), 7.43-7.56 (4H, m), 7.20-7.38 (7H, m), 6.53 (1H, d), 5.20 (2H, s), 3.78 (3H, br s), 3.07 (2H, q), 2.51 (3H, s), 1.06 (3H, t); MS(ESI): 509 (MH^+).

EXAMPLE 104

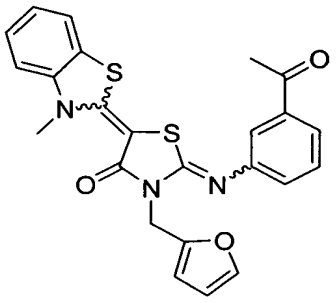
Preparation of 3-benzyl-2-benzylimino-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with benzylamine. ^{1}H-NMR ($CDCl_3$): δ 7.46-7.57 (3H, m), 7.22-7.37 (9H, m), 7.15 (1H, m), 7.03 (1H, br d), 5.09 (2H, br s), 4.49 (2H, br s), 3.85 (3H, s); MS(ESI): 444 (MH^+).

EXAMPLE 105

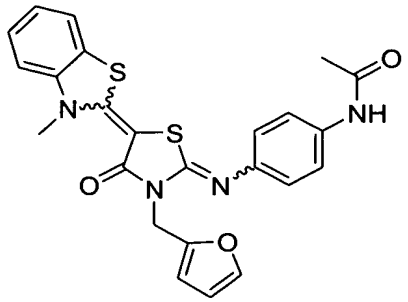
Preparation of 2-(3-acetylphenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 79 by replacing 3-picolyl isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. MS(ESI): 462 (MH^+).

EXAMPLE 106

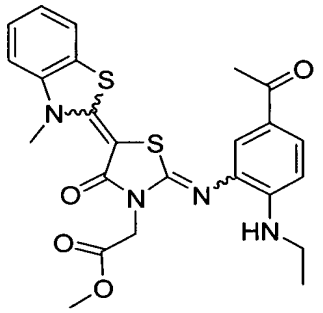
Preparation of N-{4-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylid ne)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide



The title compound was prepared in a manner similar to that described in Example 105 by replacing 3'-aminoacetophenone with 4'-aminoacetanilide. MS(ESI): 477 (MH^+).

EXAMPLE 107

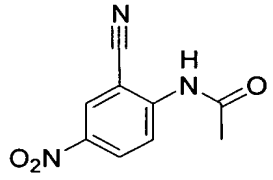
Preparation of [2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-yl]acetic acid methyl ester



The title compound was prepared in a manner similar to Example 1 by replacing 3-benzylrhodanine with rhodanine-3-acetic acid methyl ester. MS(ESI): 497 (MH^+).

EXAMPLE 108

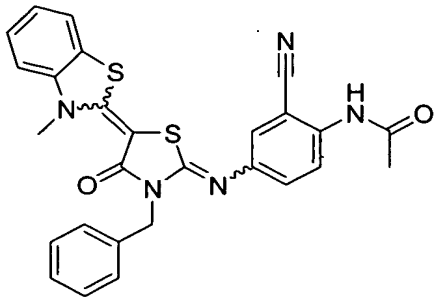
A. Preparation of 2-cyano-4-nitroacetanilide



The title compound was prepared in a manner similar to Example 80 by replacing 2-amino-5-nitropyridine with 5-nitroanthranilonitrile. ^{1}H-NMR

($CDCl_3$): δ 8.78 (1H, d), 8.49 (1H, d), 8.44 (1H, dd), 7.88 (1H, br s), 2.35 (3H, s).

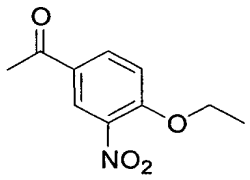
B. Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide



In a manner similar to Example 30, intermediate 2-cyano-4-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.30 (1H, d), 7.49-7.57 (4H, m), 7.27-7.38 (5H, m), 7.22 (1H, d), 7.19 (1H, m), 7.07 (1H, d), 5.14 (2H, s), 3.76 (3H, s), 2.27 (3H, s); MS(ESI): 512 (MH^+).

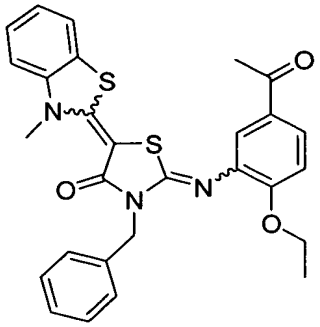
EXAMPLE 109

A. Preparation of 4'-ethoxy-3'-nitroacetophenone



To a solution of 4'-hydroxy-3'-nitroacetophenone (1.0 g, 5.5 mmol) in anhydrous DMF (20 mL) was added anhydrous K_2CO_3 (3.0 g, 22 mmol) and then bromoethane (0.49 mL, 6.6 mmol). After heating at 80°C for 20h, the reaction mixture was cooled, combined with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with water (3 x 50 mL), 1 N NaOH (50 mL) and then brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound (1.1 g, 96%) as a light brown solid, which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.41 (1H, d), 8.15 (1H, dd), 7.14 (1H, d), 4.28 (2H, q), 2.61 (3H, s), 1.52 (3H, t).

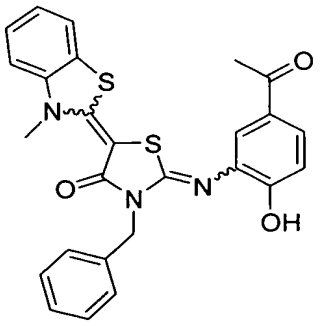
B. Preparation of 2-(5-acetyl-2-ethoxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



In a manner similar to Example 30, intermediate 4'-ethoxy-3'-nitroacetophenone was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.77 (1H, dd), 7.64-7.68 (2H, m), 7.61 (1H, d), 7.48 (1H, m), 7.25-7.36 (4H, m), 7.15 (1H, m), 6.99 (1H, d), 6.98 (1H, d), 5.20 (2H, s), 4.11 (2H, q), 3.69 (3H, s), 2.57 (3H, s), 1.43 (3H, t); MS(ESI): 516 (MH^+).

EXAMPLE 110

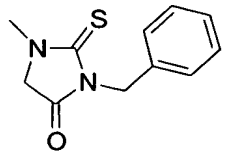
Preparation of 2-(5-acetyl-2-hydroxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



In a manner similar to Example 30, 4'-hydroxy-3'-nitroacetophenone was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 488 (MH^+).

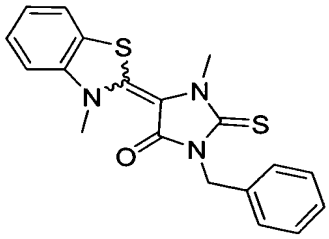
EXAMPLE 111

A. Preparation of 3-benzyl-1-methyl-2-thioxoimidazolidin-4-one



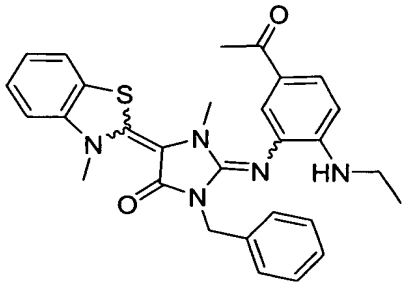
To a solution of sarcosine methyl ester hydrochloride (0.56 g, 4.0 mmol) and DBU (0.60 mL, 4.0 mmol) in anhydrous ethanol added benzyl isothiocyanate (0.53 mL, 4.0 mmol). The resulting solution was heated at reflux 16h, cooled, concentrated and chromatographed (silica gel, DCM) to give the title compound (0.88 g, quant.). ^{1}H-NMR ($CDCl_3$): δ 7.49-7.53 (2H, m), 7.28-7.35 (3H, m), 5.02 (2H, s), 4.03 (2H, s), 3.34 (3H, s).

B. Preparation of 3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxoimidazolidin-4-one



To a mixture of intermediate 3-benzyl-1-methyl-2-thioxoimidazolidin-4-one (0.33 g, 1.5 mmol) and 3-methyl-2-methylthiobenzothiazol-3-ium *p*-toluenesulfonate 0.66 g, 1.8 mmol) in anhydrous MeCN (10 mL) added dropwise TEA (0.28 mL, 2.0 mmol). After 2h the resulting product mixture was concentrated and chromatographed (silica gel, DCM) to afford the title compound (0.47 g, 85%) as an orange-yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.54-7.61 (3H, m), 7.46 (1H, m), 7.21-7.33 (5H, m), 5.19 (2H, s), 3.86 (3H, s), 3.77 (3H, s).

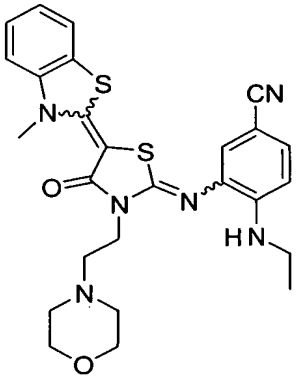
C. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-1-methyl-5-(3-methyl-3*H*-b nzothiazol-2-ylidene)imidazolidin-4-one



In a manner similar to Example 1, intermediate 3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxoimidazolidin-4-one was alkylated with methyl *p*-toluenesulfonate and condensed with 3'-amino-4'-ethylaminoacetophenone to yield the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.11 (1H, d), 7.84 (1H, dd), 7.51 (1H, dd), 7.31 (1H, m), 7.16 (1H, m), 6.95-7.12 (7H, m), 6.08 (1H, br t), 4.46 (2H, hs m), 3.99 (2H, m), 3.78 (3H, s), 3.50 (3H, s), 2.65 (3H, s), 1.06 (3H, t); MS(ESI): 512 (MH^+).

EXAMPLE 112

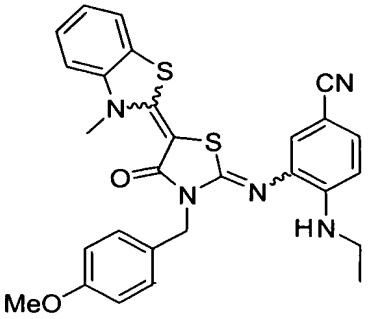
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(2-morpholin-4-ylethyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with N-(2-ethylisothiocyanate)morpholine, synthesized from N-(2-aminoethyl)morpholine and thiophosgene. ^{1}H-NMR ($CDCl_3$): δ 7.52 (1H, d), 7.32-7.37 (2H, m), 7.18-7.23 (2H, m), 7.09 (1H, d), 6.60 (^{1}H, d), 4.75 (1H, br s), 4.16 (1H, t), 3.81 (3H, s), 3.71 (4H, br s), 3.23 (2H, q), 2.76 (2H, br s), 2.60 (4H, br s), 1.29 (3H, t); MS(ESI): 521 (MH^+).

EXAMPLE 113

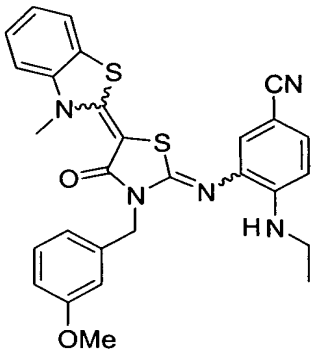
Preparation of 4-ethylamino-3-[3-(4-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 4-methoxybenzylisothiocyanate. MS(ESI): 528 (MH^+).

EXAMPLE 114

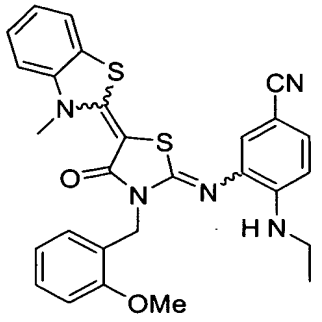
Preparation of 4-ethylamino-3-[3-(3-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-methoxybenzylisothiocyanate. ^{1}H-NMR ($CDCl_3$): δ 7.55 (1H, d), 7.37 (1H, t), 7.22-7.32 (4H, m), 7.12 (1H, d), 7.01 (2H, m), 6.86 (1H, d), 6.51 (1H, d), 5.16 (2H, s), 4.32 (1H, t), 3.84 (3H, s), 3.81 (3H, s), 3.03 (2H, q), 1.05 (3H, t); MS(ESI): 528 (MH^+). Recrystallization of the product from hot MeCN afforded crystals suitable for single-crystal X-ray diffraction. Structural analysis showed that the E-isomer had been obtained.

EXAMPLE 115

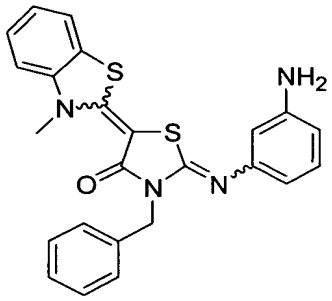
Preparation of 4-ethylamino-3-[3-(2-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylid neamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 2-methoxybenzylisothiocyanate. MS(ESI): 528 (MH^+).

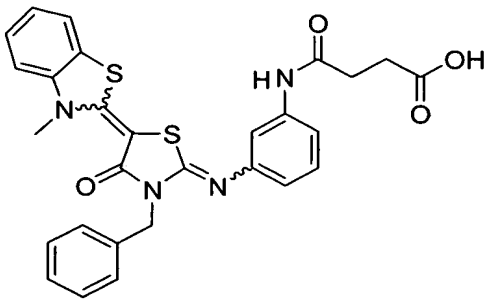
EXAMPLE 116

A. Preparation of 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,3-phenylenediamine. MS(ESI): 445 (MH^+).

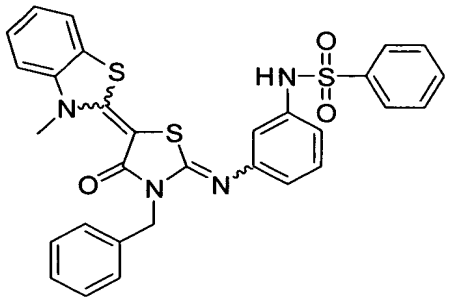
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}succinamic acid



To a 25 mL flask was added 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one (100 mg, 225 μmol), anhydrous DCM (5 mL) and $CHCl_3$ (3 mL). To the solution was added succinic anhydride (23 mg, 239 μmol). The reaction solution was allowed to stir at 50°C for 1.5h. The white precipitates were collected by filtration under reduced pressure, washed with DCM (10 mL) and hexanes (20 mL), and then dried under vacuum to give the title compound (75 mg, 61%). MS(ESI): 545 (MH^+).

EXAMPLE 117

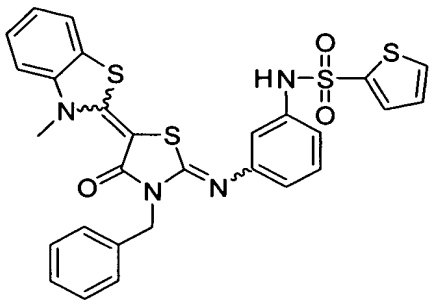
Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}benzenesulfonamide



To a 25 mL flask was added 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one (0.18 g, 0.40 mmol), anhydrous $CHCl_3$ (7 mL), benzenesulfonyl chloride (56 μL, 0.44 mmol), and TEA (0.10 mL, 0.80 mmol). The solution was stirred at 50°C for 20h. The yellow precipitates were collected by filtration under reduced pressure, washed with hexanes (30 mL), and dried under vacuum to give the title compound (49 mg, 21%) as a yellow solid. ^{1}H-NMR (DMSO-d_6): δ 7.97 (1H, s), 7.76 (2H, d), 7.53 (2H, m), 7.45 (2H, t), 7.37 (2H, d), 7.09-7.31 (8H, m), 6.81 (1H, d), 6.74 (1H, s), 6.57 (1H, d), 4.99 (2H, s), 3.72 (3H, s); MS(ESI): 585 (MH^+).

EXAMPLE 118

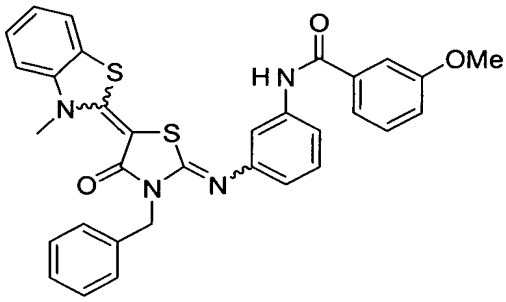
Preparation of thiophen -2-sulfonic acid {3-[3-b nzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}amide



The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with 2-(thiophene)sulfonyl chloride. MS(ESI): 591 (MH^+).

EXAMPLE 119

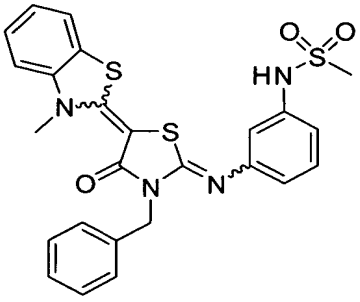
Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-3-methoxybenzamide



The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with 3-methoxybenzoyl chloride. MS(ESI): 579(MH^+).

EXAMPLE 120

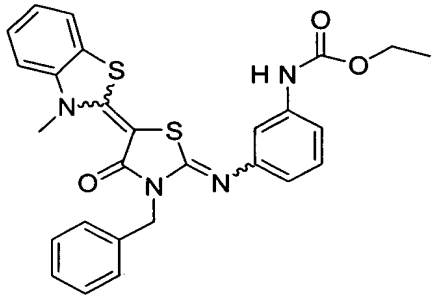
Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide



The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with methanesulfonyl choride. ^{1}H-NMR ($CDCl_3$): δ 8.88 (1H, s), 7.48 (2H, d), 7.41 (1H, d), 7.16-7.26 (5H, m), 7.09 (1H, t), 6.96 (2H, t), 6.89 (1H, m), 6.70 (1H, d), 5.05 (2H, s), 3.67 (3H, s), 2.92 (3H, s); MS(ESI): 532 (MH^+).

EXAMPLE 121

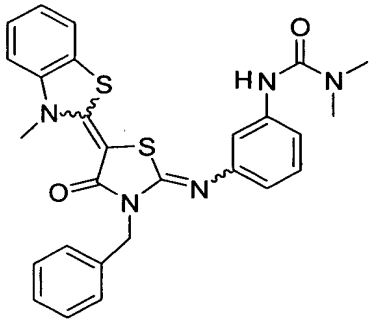
Preparation of {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester



The title compound was prepared in a manner similar to the described in Example 117 by replacing benzenesulfonyl chloride with ethyl chloroformate. MS(ESI): 517 (MH^+).

EXAMPLE 122

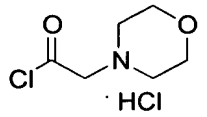
Preparation of 3-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-1,1-dimethylurea



The title compound was prepared in a manner similar to the described in Example 117 by replacing benzenesulfonyl chloride with dimethylcarbamyl chloride. MS(ESI): 523(MH^+).

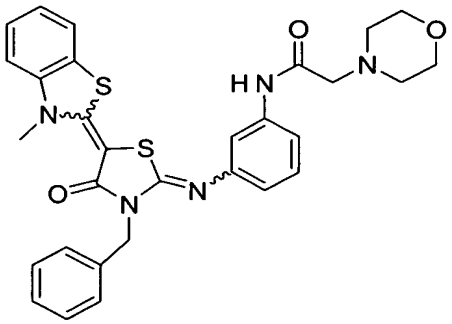
EXAMPLE 123

A. Preparation of morpholin-4-ylac tyl chloride hydrochloride



To a 100 mL flask was added morpholine (5.5 g, 63 mmol), benzene (20 mL), and ethyl chloroacetate (3.2 mL, 30 mmol). The reaction solution was allowed to stir 1h at ambient temperature. The resulting white crystalline solids were collected by filtration under reduced pressure and then transferred to a 100 mL flask along with dioxane (20 mL) and 1N NaOH (33 mL). The solution was allowed to stir at 80°C for 16h, cooled and then neutralized with 1N HCl. The aqueous solution was frozen and lyophilized to isolate the crude morpholinylacetic acid. The crude acid (2.6 g, 20 mmol) and thionyl chloride (15 mL) was added to a N_2-purged 100 mL flask. After stirring 3h the reaction solution was filtered and concentrated under reduced pressure to provide the title compound (3.1 g, 78%) as a white powder. ^{1}H-NMR (DMSO-d_6): δ 7.58 (1H, s), 3.48 (2H, s), 3.37 (4H, m), 2.76 (4H, m); ^{13}C-NMR (DMSO-d_6): δ 166.0, 63.5, 55.5, 51.8.

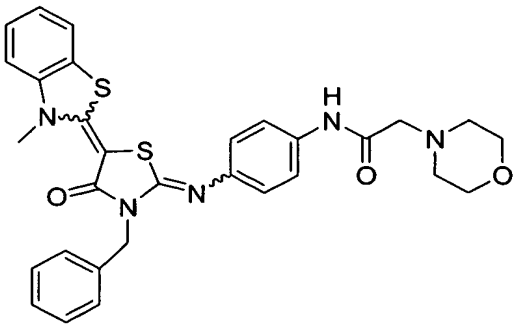
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide



The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with morpholin-4-ylacetyl chloride hydrochloride. ^{1}H-NMR ($CDCl_3$): δ 8.98 (1H, s), 7.51 (2H, d), 7.41 (1H, d), 7.34 (1H, d), 7.19-7.27 (5H, m), 7.08 (2H, m), 6.91 (1H, d), 6.70 (1H, d), 5.06 (2H, s), 3.70 (4H, t), 3.63 (3H, s), 3.07 (2H, s), 2.55 (4H, t); MS(ESI): 572 (MH^+).

EXAMPLE 124

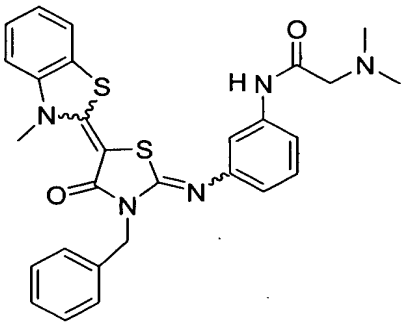
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide



The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 123. MS(ESI): 572 (MH^+).

EXAMPLE 125

Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide



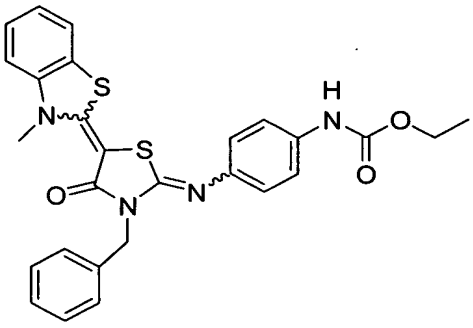
To a 25 mL flask was added N, N-dimethylglycine (500 mg, 4.85 mmol) and thionyl chloride (5 mL). The resulting solution was allowed to stir at ambient temperature under N_2 for 3h. The excess thionyl chloride was removed in vacuo to provide N, N-dimethylaminoacetyl chloride hydrochloride as a white powder.

To a solution of 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one (160 mg, 360 μmol) in chloroform (8 mL) was added N, N-dimethylaminoacetyl chloride hydrochloride (90 mg, 0.58 mmol) and TEA (150 μL, 1.1 mmol). The reaction solution was heated at reflux for 20h, cooled, and concentrated in vacuo. The crude material was chromatographed (silica gel, 0-50% EtOAc/Hex) to give the title compound (34 mg, 18%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 9.03 (1H, s), 7.50 (2H, d),

7.37 (2H, t), 7.17-7.26 (5H, m), 7.11 (1H, m), 7.05 (1H, t), 6.88 (1H, d), 6.68 (1H, d), 5.03 (2H), 3.60 (3H, s), 3.00 (2H, s), 2.28 (6H, s); MS(ESI): 530(MH^+).

EXAMPLE 126

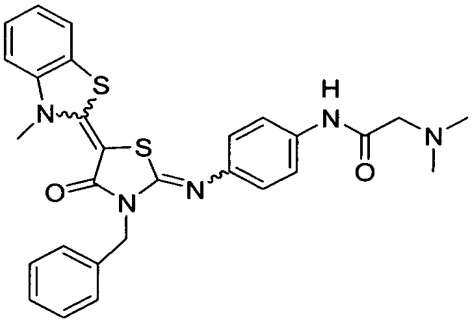
Preparation of {4-[3-benzyl-5-(3-methyl-3*H*-benzothiaz l-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester



The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 121. ^{1}H-NMR ($CDCl_3$): δ 7.49 (2H, d), 7.37 (1H, d), 7.20-7.29 (5H, m), 7.07 (1H, t), 6.87-6.95 (3H, m), 6.54 (1H, br s), 5.07 (2H, s), 4.15 (2H, q), 3.61 (3H, s), 1.24 (3H, t); MS(ESI): 517(MH^+).

EXAMPLE 127

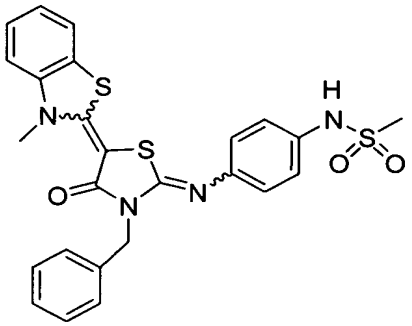
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide



The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 125. MS(ESI) 530(MH^+).

EXAMPLE 128

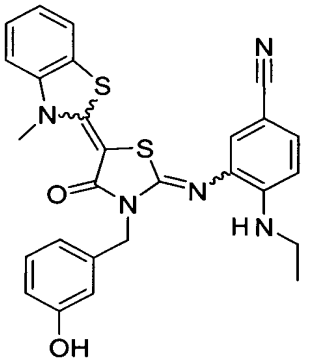
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide



The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 120. MS(ESI): 523 (MH^+).

EXAMPLE 129

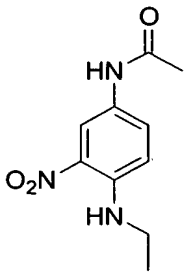
Preparation of 4-ethylamino-3-[3-(3-hydroxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



To a N_2-purged flask was added the product of Example 114 (60 mg, 0.11 mmol) and anhydrous DCM (5 mL). The solution was cooled to –78°C prior to the addition of a 1.0M solution of BBr_3 in DCM (0.50 mL). The solution was allowed to warm to ambient temperature with stirring. After 7h the solution was quenched by addition of MeOH (10 mL) and then concentrated under reduced pressure. The crude material was purified by reverse-phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H_2O (1:9 to 9:1) to provide the title compound (15 mg, 26%). ^{1}H-NMR ($CDCl_3$): δ 7.40 (1H, d), 7.35 (1H, t), 7.29 (1H, dd), 7.13-7.25 (3H, m), 6.95-7.01 (3H, m), 6.76 (1H, dd), 6.49 (1H, d), 5.08 (2H, s), 3.56 (3H, s), 3.02 (2H, q), 1.05 (3H, t); MS(ESI): 514(MH^+).

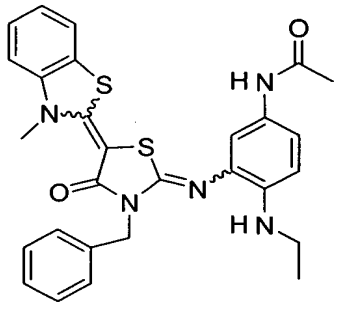
EXAMPLE 130

Preparation of 4'-ethylamino-3'-nitroacetanilide



To a solution of 4-fluoro-3-nitroaniline (2.5 g, 16 mmol) in DCM (35 mL) was added acetic anhydride (2.3 mL, 24 mmol). The solution was stirred 15min, and the resulting off-white precipitates were collected by filtration under reduced pressure. To a solution of the intermediate acetanilide in anhydrous THF (15 mL) was added a 2.0M solution of ethylamine in THF (8.0 mL). The solution was stirred at ambient temperature 14h, and the resulting precipitates were collected by filtration under reduced pressure and dried under vacuum to provide the title compound (2.4 g, 68 %). ^{1}H-NMR ($CDCl_3$): δ 8.08 (1H, d), 7.90 (1H, br s), 7.78 (1H, dd), 7.32 (1H, br s), 6.82 (1H, d), 3.35 (2H, q), 2.16 (3H, s), 1.36 (3H, t).

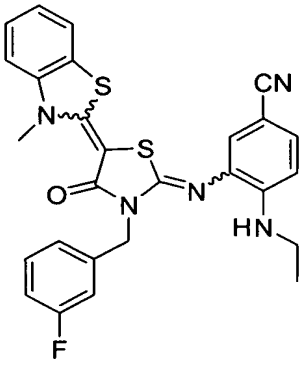
B. Preparation of 4-ethylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]acetanilide



In a manner similar to Example 30, intermediate 4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium p-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 9.58 (1H, s), 7.76 (1H, d), 7.18-7.46 (9H, m), 7.12 (1H, d), 6.47 (1H, d), 5.09 (2H, s), 3.82 (1H, br s), 3.79 (3H, s), 2.92 (2H, t), 1.98 (3H, s), 0.97 (3H, t); MS(ESI): 530(MH^+).

EXAMPLE 131

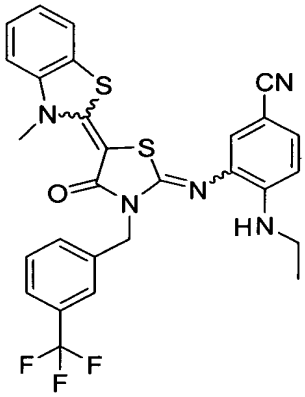
Preparation of 4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was synthesized in a manner similar or to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-fluorobenzylisothiocyanate. MS(ESI): 516 (MH^+).

EXAMPLE 132

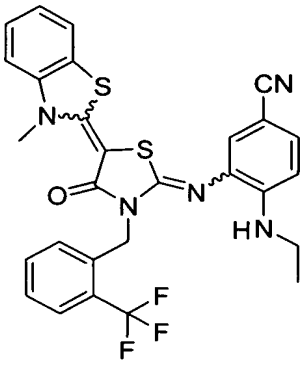
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(3-trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile



The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-(trifluoromethyl)benzylisothiocyanate. MS(ESI): 566 (MH^+).

EXAMPLE 133

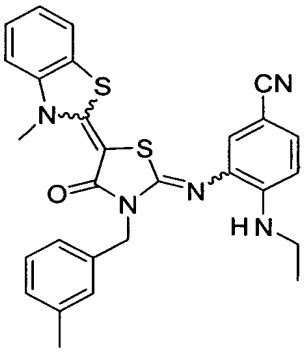
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(2-trifluoromethylb nzyl)thiazolidin-2-ylideneamino]benzonitrile



The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 2-(trifluoromethyl)benzylisothiocyanate. MS(ESI): 566 (MH^+).

EXAMPLE 134

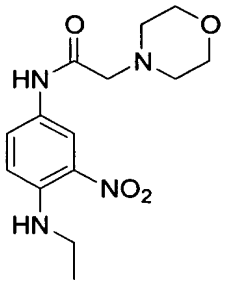
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(3-methylbenzyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-methylbenzylisothiocyanate. MS(ESI): 512(MH^+).

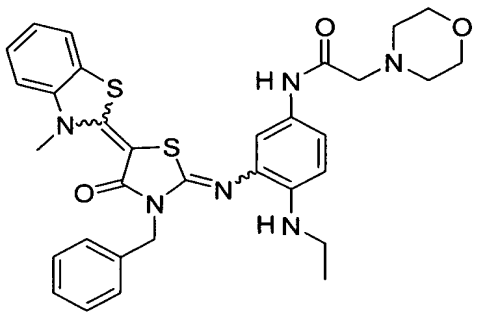
EXAMPLE 135

A. Preparation of 4'-ethylamino-2-(morpholin-4-yl)-3'-nitroacetanilid



The title compound was synthesized in a manner similar to Example 130 by replacing acetic anhydride with morpholin-4-ylacetyl chloride hydrochloride. ^{1}H-NMR ($CDCl_3$): δ8.94 (1H, s), 8.11 (1H, d), 7.88 (1H, dd), 6.83 (1H, d), 3.78 (4H, t), 3.34 (2H, q), 3.13 (2H, s), 2.62 (4H, t), 1.31 (3H, t).

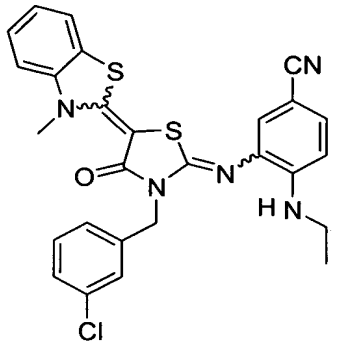
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-morpholin-4-ylacetamide



In a manner similar to Example 30, intermediate 4'-ethylamino-2-(morpholin-4-yl)-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR (CDC_3): δ 8.87 (1H, s), 7.49-7.53 (3H, m), 7.28-7.37 (5H, m), 7.19 (1H, t), 7.12 (1H, dd), 7.04 (1H, d), 6.57 (1H, d), 5.19 (2H, s), 3.79 (8H, br s), 3.16 (2H, s), 3.01 (2H, q), 2.66 (4H, br s), 1.06 (3H, t); MS(ESI): 615(MH^+).

EXAMPLE 136

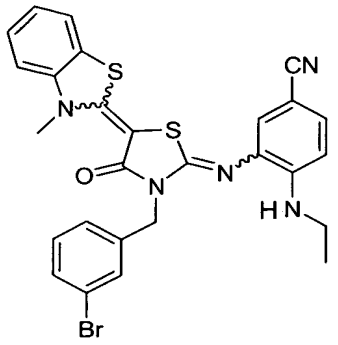
Preparation of 3-[3-(3-chlorob nzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-chlorobenzylisothiocyanate. MS(ESI): 533 (MH^+).

EXAMPLE 137

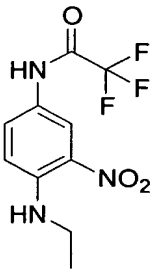
Preparation of 3-[3-(3-bromobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-bromobenzylisothiocyanate. MS(ESI): 578(MH^+).

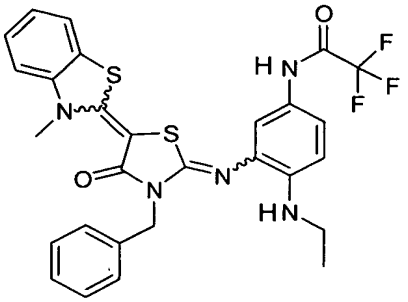
EXAMPLE 138

A. Preparation of 4'-ethylamino-3'-nitro-2,2,2-trifluoroacetanilide



The title compound was prepared in a manner similar to that described in Example 130 by replacing acetic anhydride with trifluoroacetic anhydride (TFAA). TLC (1:1 Hex/EtOAc) R_f = 0.5; MS(ESI): 278(MH^+).

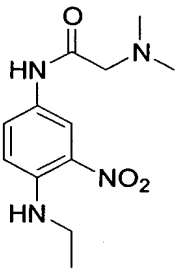
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2,2,2-trifluoroacetamide



In a manner similar to Example 30, intermediate 4'-ethylamino-3'-nitro-2,2,2-trifluoroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 584(MH^+).

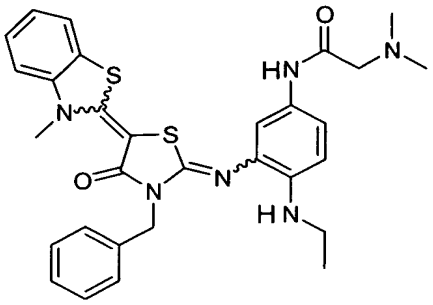
EXAMPLE 139

A. Preparation of 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide



The title compound was prepared in a similar manner as that described in Example 130 by replacing acetic anhydride with N,N-dimethylaminoacetyl chloride hydrochloride. ^{1}H-NMR ($CDCl_3$): δ 9.04 (1H, s), 8.16 (1H, d), 7.95 (1H, dd), 7.89 (1H, br s), 6.84 (1H, d), 3.35 (2H, q), 3.09 (2H, s), 2.39 (6H, s), 1.36 (3H, t); MS(ESI): 267(MH^+).

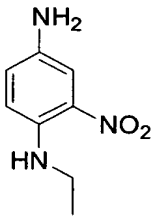
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminoph nyl}-2-dimethylaminoacetamide



In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.85 (1H, s), 7.43 (3H, t), 7.18-7.28 (5H, m), 7.10 (2H, t), 6.95 (1H, d), 6.48 (1H, d), 5.10 (2H, s), 3.71 (3H, s), 3.03 (2H, s), 2.93 (2H, q), 2.33 (6H, s), 0.97 (3H, t); MS(ESI): 584(MH^+).

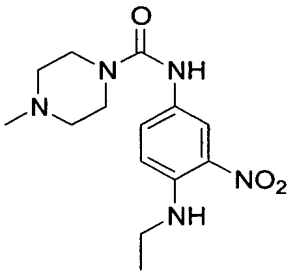
EXAMPLE 140

A. Preparation of 4-ethylamino-3-nitroaniline



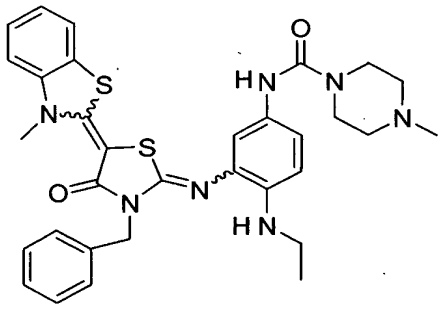
To a pressure tube was added 4-fluoro-3-nitroaniline (550 mg, 3.50 mmol) and a 2.0 M solution of ethylamine in THF (8 mL). The sealed tube was heated at 120°C for 24h. The reaction solution was cooled, diluted with EtOAc (30 mL), washed with saturated $NaHCO_3$ (2 x 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide the title compound (625 mg, 98%) as a purple solid. ^{1}H-NMR ($CDCl_3$): δ 7.72 (1H, br s), 7.49 (1H, d), 6.96 (1H, dd), 6.74 (1H, d), 3.45 (2H, br s), 3.30 (2H, m), 1.33 (3H, t).

B. Preparation of 4-methylpiperazine-1-carboxylic acid (4-ethylamino-3-nitro-phenyl)amide



To a 100 mL flask was added 4-ethylamino-3-nitroaniline (625 mg, 3.45 mmol), chloroform (30 mL), and triphosgene (341 mg, 1.15 mmol). To the solution was added saturated $NaHCO_3$ (30 mL), and the biphasic mixture was stirred for 30 min. The organic phase was partitioned, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (16 mL), and 4-methylpiperizine (291 mg, 2.90 mmol) was added. The solution was stirred at 40°C for 1h, cooled and concentrated under reduced pressure to provide the title compound (1.0 g, 94 %) as a red solid. ^{1}H-NMR ($CDCl_3$): δ 7.91 (1H, d), 7.84 (1H, t), 7.61 (1H, dd), 6.95 (1H, s), 6.73 (1H, d) 3.52 (4H, t), 3.31 (2H, m), 2.42 (4H, t), 2.32 (3H, s), 1.34 (3H, t); MS(ESI): 308(MH^+).

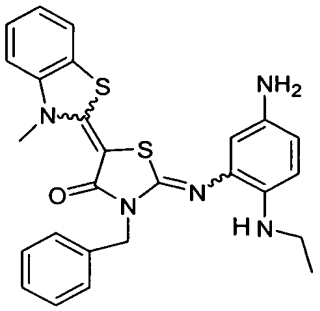
C. Preparation of 4-methylpiperazine-1-carboxylic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}amide



In a manner similar to Example 30, intermediate 4-methylpiperazine-1-carboxylic acid (4-ethylamino-3-nitro-phenyl)amide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 614(MH^+).

EXAMPLE 141

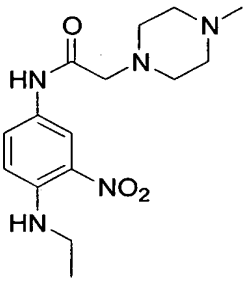
Preparation of 2-(5-amino-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-b nzothiazol-2-ylidene)thiazolidin-4-one



To the product of Example 138 (0.15 g, 0.26 mmol) in MeOH (30 mL) was added H_2O (6 mL) and fine mesh K_2CO_3 (0.30 g, 1.5 mmol), and the solution was stirred 24h at 55°C. The reaction mixture was cooled, diluted with EtOAc (30 mL), washed with H_2O (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by reverse-phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H_2O (1:9 to 9:1) to provide the title compound (2 mg). MS(ESI): 488(MH^+).

EXAMPLE 142

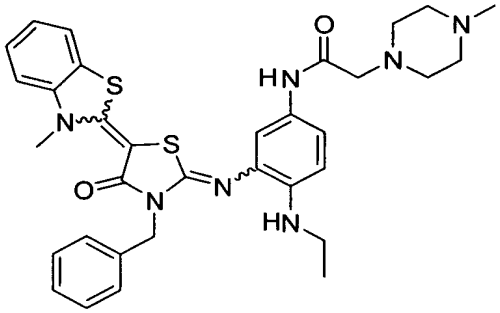
A. Preparation of 4'-ethylamino-2-(4-methylpiperazin-1-yl)-3'-nitroacetanilide



To a 100 mL flask was added 4-fluoro-3-nitroaniline (0.83 g, 5.3 mmol), DCM (30 mL), bromoacetyl chloride (0.53 mL, 6.4 mmol), and TEA (0.74 mL, 5.3 mmol). The reaction solution was stirred at room temperature 2h and then quenched with saturated $NaHCO_3$ (20 mL). The organic phase was partitioned, dried over Na_2SO_4, filtered under vacuum, and concentrated under reduced pressure. The resulting amide (1.31 g, 4.73 mmol) was added to a 100 mL flask along with MeCN (20 mL), 4-methylpiperizine (0.53 mL, 4.7 mmol), and K_2CO_3 (655 mg, 4.74 mmol). The reaction slurry was stirred 14h

at 35°C prior to removal of excess K_2CO_3 by vacuum filtration. The filtrate was concentrated under reduced pressure, and the crude residue was chromatographed (SiO_2, hexane/EtOAc) to provide 400 mg of intermediate amide. In a manner similar to that described in Example 31, the intermediate amide was treated with ethylamine to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 9.66 (1H, s), 8.44 (1H, m), 8.05 (1H, m), 7.17 (1H, t), 3.25 (2H, s), 3.19 (4H, m), 3.14 (2H, m), 2.88 (4H, m), 2.53 (3H, 2), 1.38 (3H, t); MS(ESI): 322(MH^+).

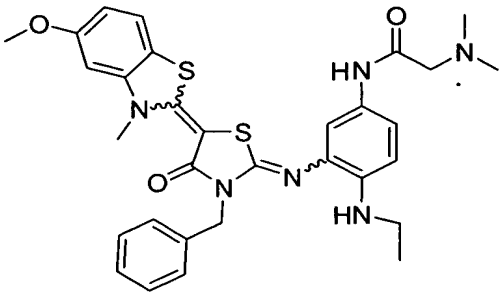
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-(4-methylpiperazin-1-yl)acetamide



In a manner similar to Example 30, intermediate 4'-ethylamino-2-(4-methylpiperazin-1-yl)-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluene sulfonate to afford the title compound. MS(ESI): 628(MH^+).

EXAMPLE 143

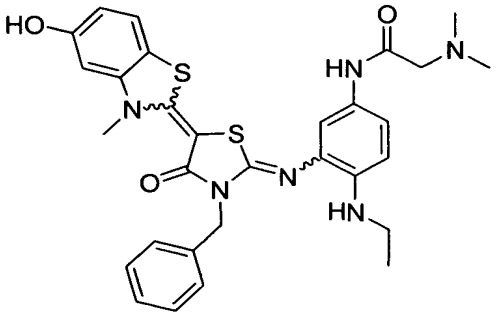
Preparation of N-{3-[3-benzyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide



The title compound was prepared in a manner similar to Example 1 by replacing 2-(methylthio)benzothiazole with 2-mercapto-5-methoxybenzothiazole and by replacing aniline with 3'-amino-2-dimethylamino-4'-ethylaminoacetanilide. MS(ESI): 603(MH^+).

EXAMPLE 144

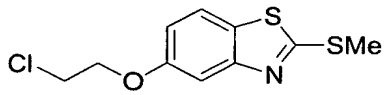
Preparation of N-{3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide



The title compound was prepared from the product of Example 143 in a manner similar to that described in Example 129. MS(ESI): 589 (MH^+).

EXAMPLE 145

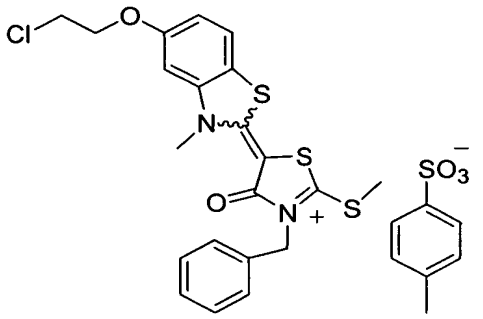
A. Preparation of 5-(2-chloroethoxy)-2-methylthio-benzothiazole



To a 250 mL flask was added 2-mercapto-5-methoxybenzothiazole (5.1 g, 26 mmol), MeCN (63 mL), methyl *p*-toluenesulfonate (4.8 g, 26 mmol) and TEA (4.4 mL, 31 mmol). After stirring 16h at ambient temperature, the solution was concentrated under reduced pressure. The crude material was diluted with EtOAc (200 mL), washed with water (2 x 75 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting viscous oil was dissolved in DCM (40 mL), and transferred to an argon-purged 250 mL flask. The solution was cooled to –78°C prior to the addition of a 1.0 M BBr_3 solution in DCM (64 mL). The reaction suspension was allowed to warm to room temperature. After 16h the reaction solution was cooled to –78°C and quenched by addition of MeOH (100 mL). The resulting precipitates were isolated by vacuum filtration to yield 5-hydroxy-2-methylthio-benzothiazole (3.9 g, 76%) as a white solid.

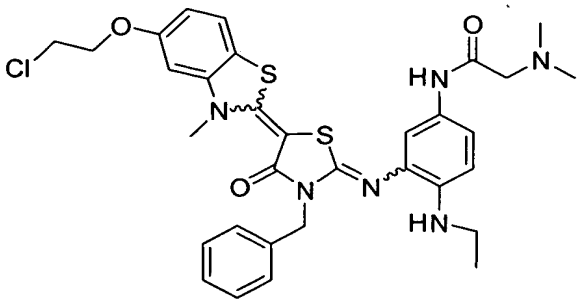
To a solution of 5-hydroxy-2-methylthio-benzothiazole (2.1 g, 11 mmol) in anhydrous DMF (25 mL) was added bromo-2-chloroethane (4.4 mL, 53 mmol) and powdered K_2CO_3 (7.3 g, 53 mmol). The reaction slurry was heated at 70°C for 13h. The slurry was filtered under vacuum and the filtrate was concentrated under reduced pressure. The crude material was chromatographed (SiO_2, 0-20% EtOAc/Hex) to afford the title compound (1.2 g, 46%). ^{1}H-NMR ($CDCl_3$): δ 7.62 (1H, d), 7.39 (1H, d), 6.97 (1H, dd), 4.29 (2H, t), 3.85 (2H, t), 2.79 (3H, s); MS(ESI): 259(MH^+).

B. Preparation of 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate



The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 5-(2-chloroethoxy)-2-methylthio-benzothiazole. ^{1}H-NMR (DMSO-d_6): δ 8.08 (1H, d), 7.65 (1H, d), 7.36-7.53 (7H, m), 7.22 (1H, dd), 7.09 (1H, d), 5.38 (2H, s), 4.45 (2H, t), 4.25 (3H, s), 4.03 (2H, t), 3.01 (3H, s), 2.28 (3H, s) MS(ESI): 463 (M^+ – *p*-toluenesulfonate).

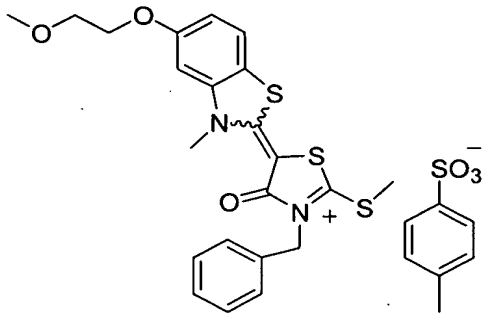
C. Preparation of N-(3-{3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide



In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 651(MH^+).

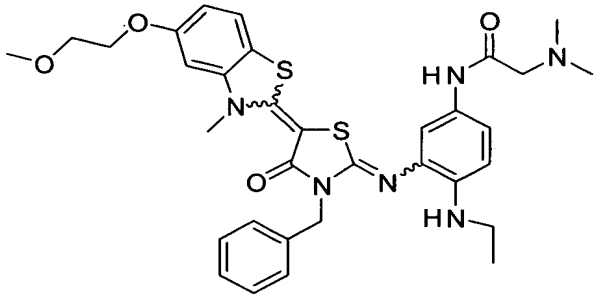
EXAMPLE 146

A. Preparation of 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate



The title compound was synthesized in a manner similar to that described in Example 145 by replacing bromo-2-chloroethane with 2-chloroethyl methylether. MS(ESI): 459 (M^+ – *p*-toluenesulfonate).

B. Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide

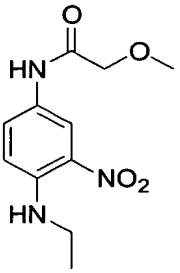


In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 9.08 (1H, s), 7.46 (2H, d), 7.27-7.35 (5H, m), 7.16 (1H, dd), 6.69 (1H, dd), 6.62 (1H, d), 6.51 (1H, d), 5.14 (2H, s), 4.13 (2H, t), 3.75 (2H, t),

3.71 (2H, s), 3.44 (3H, s), 3.19 (2H, s), 2.94 (2H, q), 2.46 (6H, s), 1.02 (3H, t); MS(ESI): 647(MH^+).

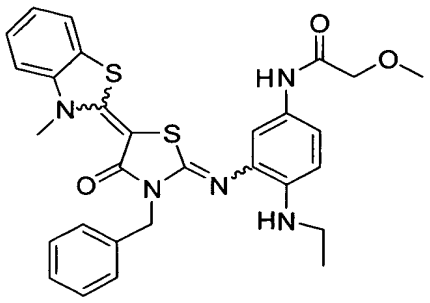
EXAMPLE 147

A. Preparation of 4'-ethylamino-2-methoxy-3'-nitroacetanilide



The title compound was prepared in a similar manner as that described in Example 130 by replacing acetic anhydride with methoxyacetyl chloride. ^{1}H-NMR ($CDCl_3$): δ 8.20 (1H, d), 8.17 (1H, br s), 7.88 (1H, dd), 6.68 (1H, d), 4.03 (2H, s), 3.52 (3H, s), 3.37 (2H, q), 1.62 (2H, br s), 1.38 (3H, t).

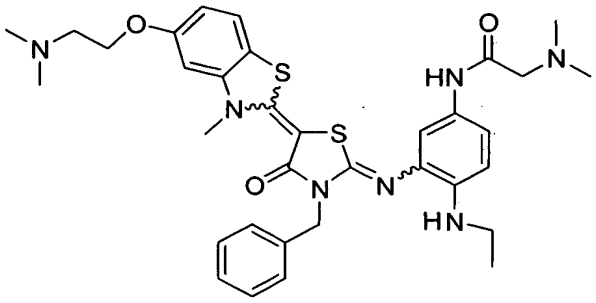
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-methoxyacetamide



In a manner similar to Example 30, intermediate 4'-ethylamino-2-methoxy-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.99 (1H, s), 7.39-7.44 (3H, m), 7.17-7.28 (5H, m), 7.05-7.11 (2H, m), 6.94 (1H, d), 6.50 (1H, d), 5.08 (2H, s), 3.92 (2H, s), 3.66 (3H, s), 3.41 (3H, s), 2.91 (2H, q), 0.96 (3H, t); MS(ESI): 560(MH^+).

EXAMPLE 148

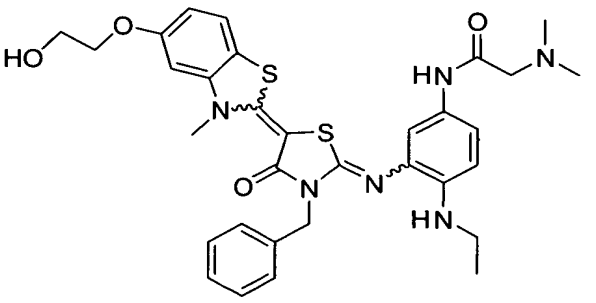
Preparation of N-(3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dim thylaminoacetamide



To a pressure tube was added the product of Example 145 (150 mg, 0.23 mmol), tetra-*n*-butylammonium iodide (85 mg, 0.23 mmol), and 2.0 M solution of dimethylamine in THF (6 mL). The tube was sealed and heated at 65°C for 14h. The solution was cooled and concentrated under reduced pressure, and the crude material was purified by chromatography (silica gel, 0-20% MeOH/DCM) to provide the title compound (30 mg, 20%). ^{1}H-NMR ($CDCl_3$): δ 8.83 (1H, s), 7.45 (2H, d), 7.22-7.34 (5H, m), 7.11 (1H, dd), 6.71 (1H, dd), 6.63 (1H, d), 6.52 (1H, d), 5.14 (2H, s), 4.12 (2H, t), 3.70 (3H, s), 3.04 (2H, s), 2.97 (2H, q), 2.82 (2H, t), 2.40 (6H, s), 2.35 (6H, s), 1.02 (3H, t); MS(ESI): 660(MH^+).

EXAMPLE 149

Preparation of N-(3-{3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylamino-acetamide

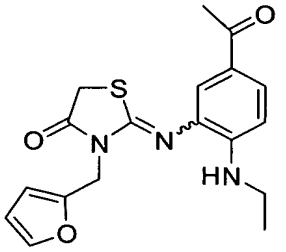


To an 8 mL vial was added the product of Example 145 (100 mg, 0.15 mmol), anhydrous DMF (5 mL), and tetra-n-butylammonium iodide (570 mg, 1.54 mmol). The solution was heated at 75°C for 4h prior to the addition of

sodium acetate (250 mg, 3.08 mmol). The reaction solution was then heated 16h at 75°C. To the solution was added MeOH (2 mL), 5M aqueous NaOH (1 mL) and H_2O (1 mL). After heating at 50°C for 5h, the reaction mixture was cooled, neutralized with conc HCl and concentrated under reduced pressure. The residue was taken up into DCM (50 mL), and the organic phase was washed with water (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was chromatographed (SiO_2, 0-10% MeOH/DCM) to provide the title compound (5 mg, 5%). ^{1}H NMR (MeOH-d_4): δ 8.92 (1H, s), 7.11-7.26 (7H, m), 6.97 (1H, dd), 6.66 (1H, dd), 6.60 (1H, d), 6.44 (1H, d), 5.01 (2H, s), 3.96 (2H, t), 3.77 (2H, t), 3.62 (3H, s), 3.00 (2H, s), 2.82 (2H, q), 2.28 (6H, s), 0.89 (3H, t); MS(ESI) 633(MH^+).

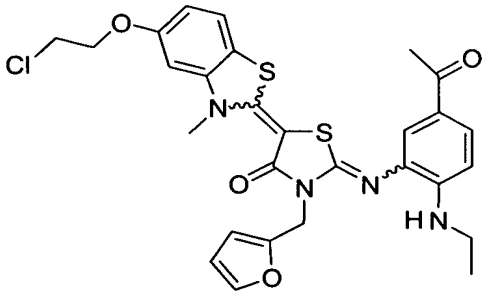
EXAMPLE 150

A. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-thiazolidin-4-one



The title compound was prepared from furfuryl isothiocyanate and 3'-amino-4'-(ethylamino)acetophenone in a manner similar to that described in Example 52. ^{1}H-NMR ($CDCl_3$): δ 7.73 (1H, dd), 7.61 (1H, s), 7.38 (1H, s), 6.59 (1H, d), 6.43 (1H, d), 6.36 (1H, m), 5.06 (2H, s), 3.88 (2H, s), 3.21 (2H, q), 2.50 (3H, s), 1.27 (3H, t); MS(ESI): 358 (MH^+).

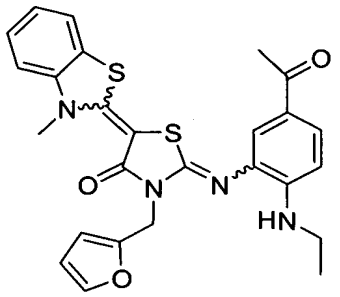
B. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one



In a manner similar to Example 45, intermediate 5-(2-chloroethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with the above 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-thiazolidin-4-one. MS(ESI): 583 (MH^+).

EXAMPLE 151

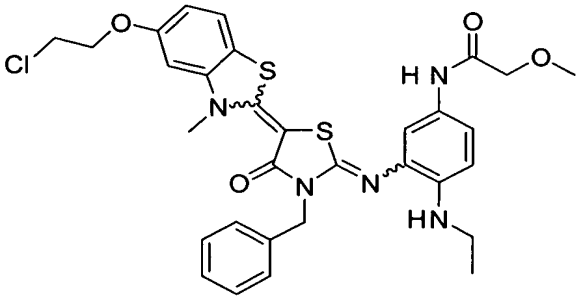
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was synthesized in a manner similar to that described in Example 82 by replacing 3-picolyl isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. ^{1}H-NMR ($CDCl_3$): δ 7.70-7.74 (2H, m), 7.52 (1H, d), 7.33-7.39 (2H, m), 7.20 (1H, t), 7.06 (1H, d), 6.68 (1H, d), 6.50 (1H, d), 6.35 (1H, m), 5.24 (2H, s), 3.76 (3H, s), 3.23 (2H, q), 2.49 (3H, s), 1.28 (3H, t); MS(ESI): 505 (MH^+).

EXAMPLE 152

Preparation of N-(3-{3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide

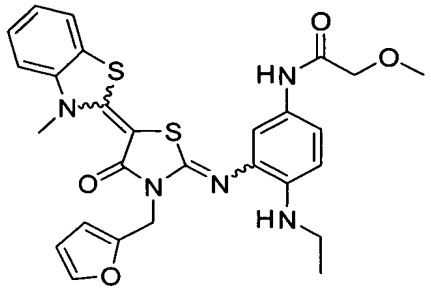


In a manner similar to Example 30, intermediate 4'-ethylamino-2-methoxy-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-

oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 638(MH^+).

EXAMPLE 153

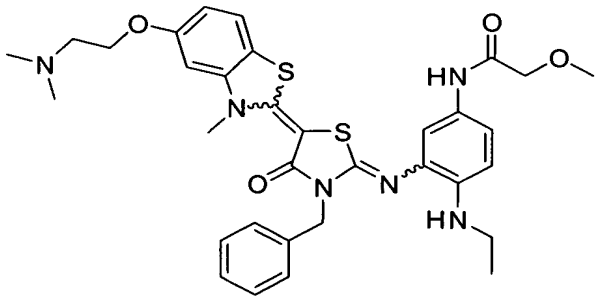
Preparation of N-{4-ethylamino-3-[3-furan-2-ylm thyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-methoxyacetamide



The title compound was prepared in a manner similar to that described in Example 84 by replacing 3-amino-4-(ethylamino)benzonitrile with 3'-amino-4'-ethylamino-2-methoxyacetanilide. ^{1}H-NMR ($CDCl_3$): δ 8.07 (1H, s), 7.50 (1H, dd), 7.37 (1H, d), 7.29-7.34 (2H, m), 7.16 (2H, m), 7.02 (1H, d), 6.66 (1H, br s), 6.45 (1H, d), 6.32 (1H, m), 5.15 (2H, s), 3.99 (2H, s), 3.75 (3H, s), 3.51 (3H, s), 3.13 (2H, q), 1.23 (3H, t); MS(ESI): 550 (MH^+).

EXAMPLE 154

Preparation of N-(3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide

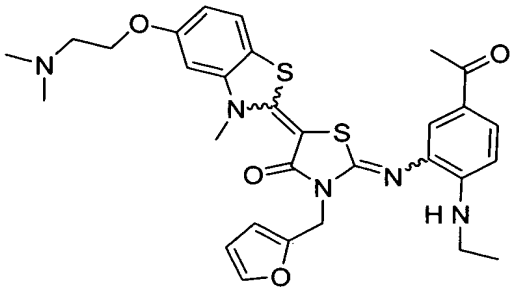


The title compound was prepared from the product of Example 152 in a manner similar to that described in Example 148. ^{1}H-NMR ($CDCl_3$): δ 8.03 (1H, s), 7.48 (2H, d), 7.24-7.37 (5H, m), 7.14 (1H, dd), 6.74 (1H, dd), 6.65 (1H, d), 6.53 (1H, d), 5.16 (2H, s), 4.13 (2H, t), 4.00 (2H, s), 3.72 (3H, s), 3.48

(3H, s), 2.99 (2H, q), 2.81 (2H, t), 2.39 (6H, s), 1.03 (3H, t); MS(ESI): 647(MH^+).

EXAMPLE 155

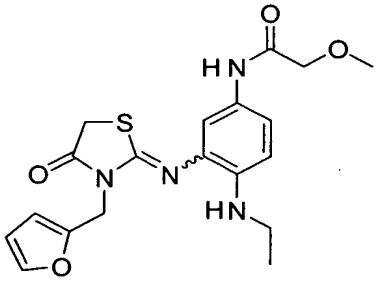
Preparation of 2-(5-acetyl-2-ethylaminoph nylimino)-5-[5-(2-dimethylamino-ethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one



The title compound was prepared from the product of Example 150 in a manner similar to that described in Example 148. ^{1}H-NMR ($CDCl_3$): δ 7.67-7.72 (2H, m), 7.37 (1H, s), 7.35 (1H, d), 6.76 (1H, dd), 6.64 (1H, d), 6.57 (1H, d), 6.45 (1H, d), 6.34 (1H, dd), 5.18 (2H, s), 4.89 (1H, t), 4.10 (2H, t), 3.71 (3H, s), 3.22 (2H, m), 2.75 (2H, m), 2.51 (3H, s), 2.35 (6H, s), 0.97 (3H, t); MS(ESI): 592(MH^+).

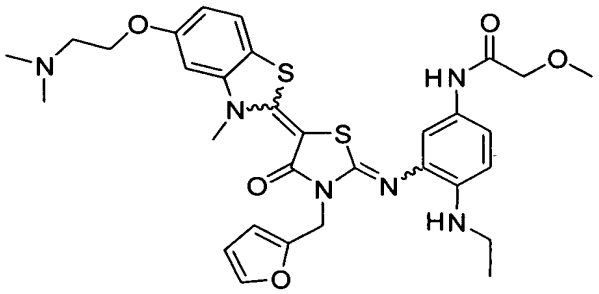
EXAMPLE 156

A. Preparation of N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide



The title compound was synthesized from 2-furfuryl isothiocyanate and 3'-amino-4'-ethylamino-2-methoxyacetanilide in a manner similar to that described in Example 52. MS(ESI): 403 (MH^+).

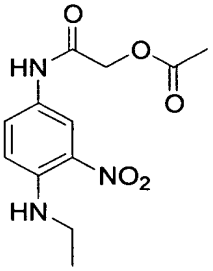
B. Preparation of N-(3-{5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide



In a manner similar to Example 45, intermediate 5-(2-chloroethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with the above N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide. The resulting product was transformed into the title compound following the procedure outlined in Example 148. MS(ESI): 583 (MH^+).

EXAMPLE 157

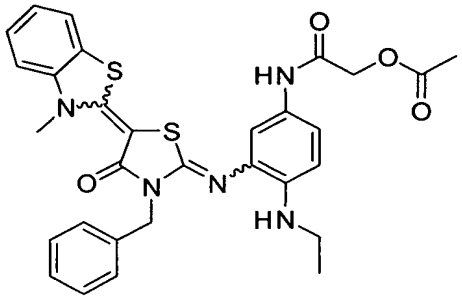
A. Preparation of 2-acetoxy-4'-ethylamino-3'-nitroacetanilide



To a 100 mL flask was added 4-ethylamino-3-nitroaniline (1.1 g, 6.3 mmol) and anhydrous $CHCl_3$ (45 mL). The solution was cooled to 0°C prior to the addition of bromoacetyl chloride (0.62 mL, 7.5 mmol) and TEA (1.7 mL, 13 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm to ambient temperature over 1h before the solvent was removed under reduced pressure. The crude material was chromatographed (SiO_2, 0-40% EtOAc/Hex) to provide the intermediate acetanilide (540 mg, 1.8 mmol) as a red solid. To a solution of the intermediate in anhydrous DMF (25 mL) was added sodium acetate (1.41 g, 17.2 mmol). The suspension was heated at 100°C for 4h. After cooling, the reaction mixture was diluted with EtOAc (25 mL), and the excess sodium acetate was removed by filtration under reduced

pressure. The filtrate was concentrated under reduced pressure to provide the title compound (420 mg). ^{1}H-NMR ($CDCl_3$): δ 8.13 (1H, br s), 8.11 (1H, d), 7.90 (1H, br s), 7.79 (1H, dd), 6.80 (1H, d), 4.68 (2H, s), 3.33 (2H, m), 2.21 (3H, s), 1.35 (3H, t); MS(ESI): 282 (MH^+).

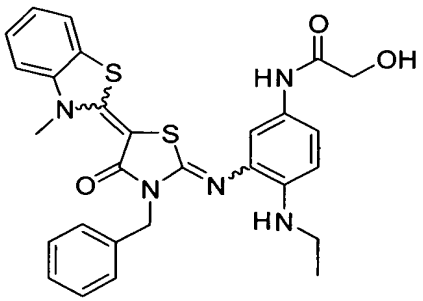
B. Preparation of acetic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenylcarbamoyl}methyl ester



In a manner similar to Example 30, intermediate 2-acetoxy-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.73 (1H, br s), 7.44-7.51 (3H, m), 7.23-7.34 (5H, m), 7.16 (1H, t), 7.08 (1H, dd), 7.00 (1H, d), 6.56 (1H, d), 5.15 (2H, s), 4.67 (2H, s), 3.74 (3H, s), 2.98 (2H, q), 2.20 (3H, s), 1.00 (3H, t); MS(ESI): 588(MH^+).

EXAMPLE 158

Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-hydroxyacetamide

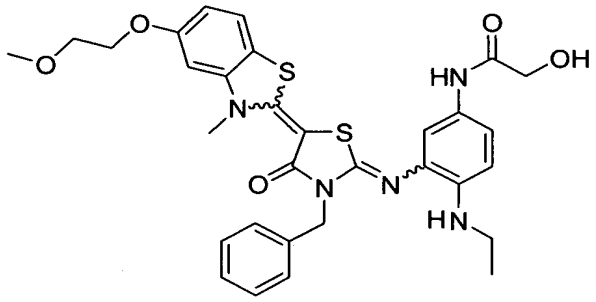


To a 50 mL flask was added the product of Example 157 (0.19 g, 0.32 mmol), $CHCl_3$ (5 mL), MeOH (10 mL), water (2 mL), and potassium carbonate (0.22 g, 1.6 mmol). After 4h the reaction mixture was diluted with $CHCl_3$ (40

mL), and the organic phase was partitioned, washed with water (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude sample was chromatographed (silica gel, 0-10% MeOH/DCM) to afford the title compound (37 mg, 21%). ^{1}H-NMR ($CDCl_3$): δ 8.14 (1H, s), 7.42-7.48 (3H, m), 7.27-7.33 (5H, m), 7.15 (1H, t), 7.09 (1H, dd), 6.99 (1H, d), 6.56 (1H, d), 5.15 (2H, s), 4.14 (2H, s), 3.71 (3H, s), 2.95 (2H, q), 0.99 (3H, t); MS(ESI): 546(MH^+).

EXAMPLE 159

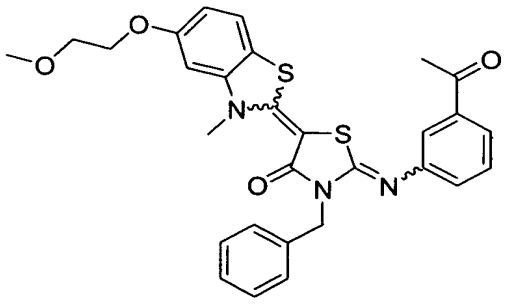
Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-hydroxyacetamide



In a manner similar to Example 30, intermediate 2-acetoxy-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford an intermediate thiazolidinone, which was hydrolyzed in a manner similar to Example 158 to provide the title compound. MS(ESI): 620(MH^+).

EXAMPLE 160

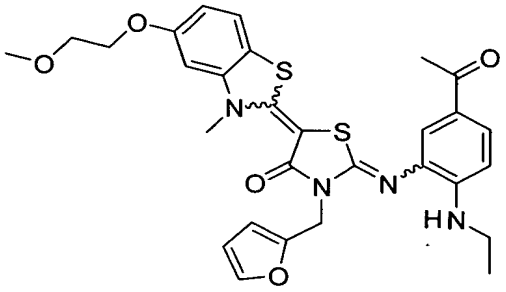
Preparation of 2-(3-acetylphenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one



The title compound was synthesized in a manner similar to that described in Example 146 by condensing 3'-aminoacetophenone with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate. ^{1}H-NMR ($CDCl_3$): δ 7.75 (1H, d), 7.60-7.64 (3H, m), 7.28-7.50 (6H, m), 7.24 (1H, d), 6.85 (1H, m), 5.21 (2H, s), 4.18 (2H, m), 3.80 (2H, m), 3.70 (3H, s), 3.48 (3H, s), 2.65 (3H, s); MS(ESI): 546(MH^+).

EXAMPLE 161

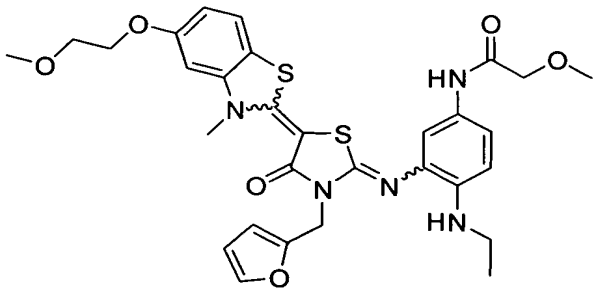
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 150 by replacing 5-(2-chloroethoxy)-2-(methylthio)benzothiazole with 5-(2-methoxyethoxy)-2-(methylthio)benzothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.69 (1H, dd), 7.66 (1H, d), 7.34-7.37 (2H, m), 6.76 (1H, dd), 6.65 (1H, d), 6.59 (1H, d), 6.45 (1H, d), 6.33 (1H, m), 5.18 (2H, s), 4.14 (2H, m), 3.75 (2H, m), 3.70 (3H, s), 3.44 (3H, s), 3.20 (2H, q), 2.51 (3H, s), 1.26 (3H, t); MS(ESI): 579(MH^+).

EXAMPLE 162

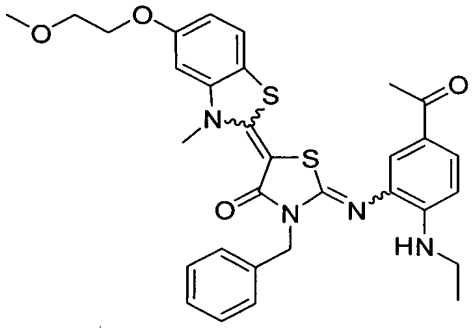
Preparation of N-(4-ethylamino-3-{3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}phenyl)-2-methoxyacetamide



In a manner similar to Example 156, 5-(2-methoxyethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with intermediate N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide. ^{1}H-NMR ($CDCl_3$): δ 8.09 (1H, s), 7.28-7.38 (3H, m), 7.15 (1H, dd), 6.76 (1H, dd), 6.64 (1H, d), 6.44 (1H, d), 6.33 (1H, m), 5.16 (2H, s), 4.14 (2H, m), 4.01 (2H, s), 3.77 (2H, m), 3.72 (3H, s), 3.51 (3H, s), 3.44 (3H, s), 3.15 (2H, q), 1.23 (3H, t); MS(ESI): 624(MH^+).

EXAMPLE 163

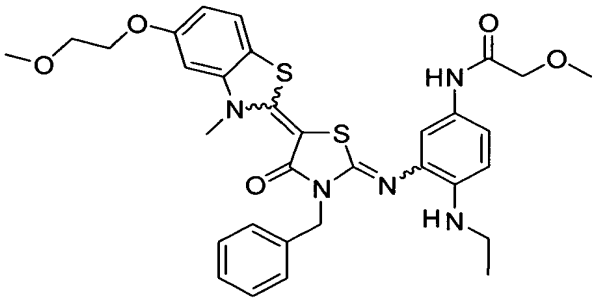
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one



The title compound was synthesized in a manner similar to that described in Example 146 by condensing 3'-amino-4'-(ethylamino)acetophenone with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate. MS(ESI): 546(MH^+).

EXAMPLE 164

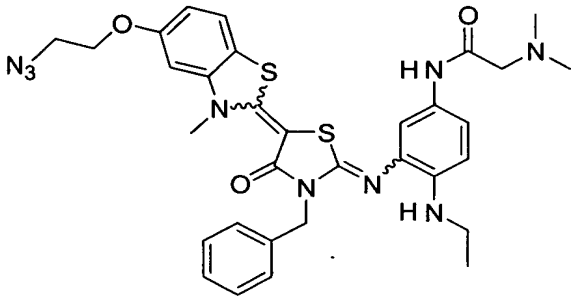
Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide



The title compound was synthesized in a manner similar to that described in Example 146 by replacing 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide with 4'-ethylamino-2-methoxy-3'-nitroacetanilide. MS(ESI): 634(MH^+).

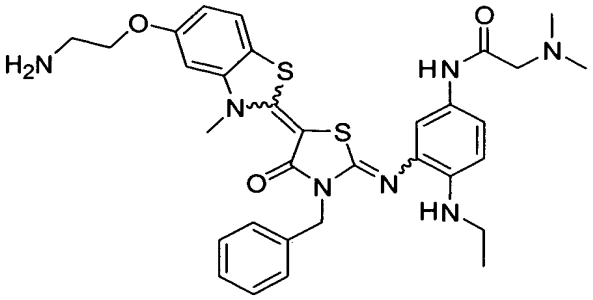
EXAMPLE 165

A. Preparation of N-(3-{5-[5-(2-azidoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide



To a 50 mL flask was added the product of Example 145 (225 mg, 345 μmol), anhydrous DMF (8mL), sodium azide (112 mg, 1.73 mmol), and sodium iodide (15 mg, 103 μmol). The reaction slurry was heated at 70 °C for 6h under N_2. The reaction mixture was diluted with EtOAc (70 mL), washed with H_2O (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the title compound. MS(ESI): 658(MH^+).

B. Preparation of N-(3-{5-[5-(2-aminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide

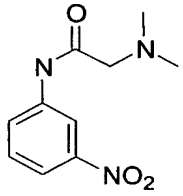


To a solution of the above N-(3-{5-[5-(2-azidoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide (0.34 mmol) in THF (13 mL) was added triphenylphosphine (100 mg, 380 mmol) and H_2O (20 mL). The

solution was stirred 48h at room temperature. The solvent was removed under reduced pressure, and the crude material was chromatographed (silica gel, 0-5% MeOH/DCM) to afford the title compound (157 mg, 72% overall). ^{1}H-NMR ($CDCl_3$): δ 8.85 (1H, s), 7.48 (2H, d), 7.27-7.37 (5H, m), 7.13 (1H, dd), 6.74 (1H, dd), 6.60 (1H, d), 6.55 (1H, d), 5.17 (2H, s), 4.03 (2H, t), 3.73 (3H, s), 3.11 (2H, t), 3.06 (2H, s), 3.00 (2H, q), 2.37 (6H, s), 1.39 (2H, t), 1.04 (3H, t); MS(ESI): 631(MH^+).

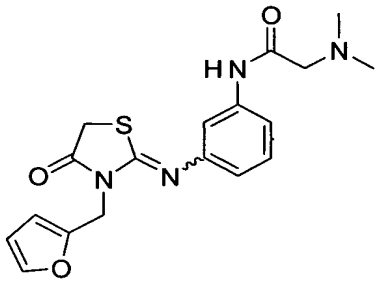
EXAMPLE 166

A. Preparation of 2-dimethylamino-3'-nitroacetanilide



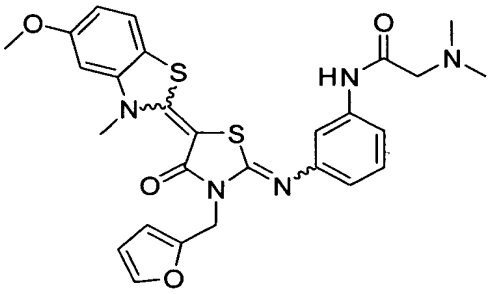
The title compound was prepared from 3-nitroaniline in a manner similar to that described in Example 139. ^{1}H-NMR ($CDCl_3$): δ 9.04 (1H, br s), 8.39 (1H, t), 8.06 (1H, dd), 7.96 (1H, dd), 7.50 (1H, t), 3.13 (2H, s), 2.41 (6H, s).

B. Prepration of 2-dimethylamino-N-[3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]acetamide



In a manner similar to that described in Example 52, the title compound was prepared from 2-furfuryl isothiocyanate and 3'-amino-2-(dimethylamino)acetanilide, derived from 2-dimethylamino-3'-nitroacetanilide. MS(ESI): 373(MH^+).

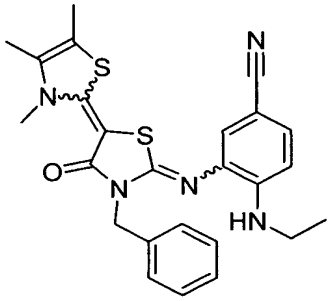
C. Preparation of 2-dimethylamino-N-{3-[3-furan-2-ylmethyl-5-(5-methoxy-3-methyl-3*H*-b nzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-phenyl}acetamide



In a manner similar to Example 45, 2-mercapto-5-methoxybenzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with 2-dimethylamino-N-[3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)-phenyl]acetamide. MS(ESI): 550 (MH^+).

EXAMPLE 167

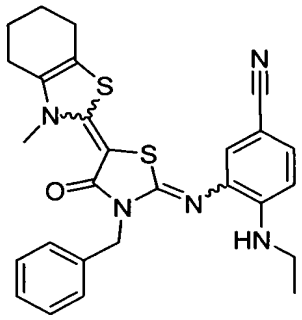
Preparation of 3-(3'-benzyl-3,4,5-trimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-2-butanone. MS(ESI): 476 (MH^+).

EXAMPLE 168

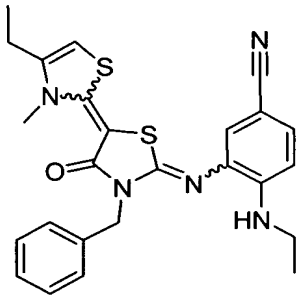
Preparation of 3-[3-benzyl-5-(3-m thyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminob nzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chlorocyclohexanone. MS(ESI): 502 (MH^+).

EXAMPLE 169

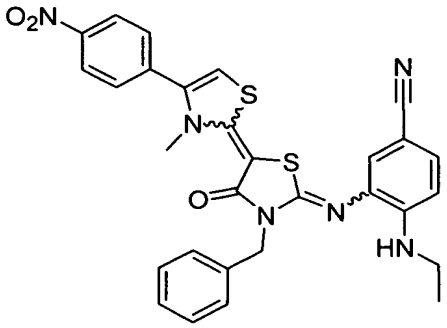
Preparation of 3-(3'-benzyl-4-ethyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-bromo-2-butanone. MS(ESI): 476 (MH^+).

EXAMPLE 170

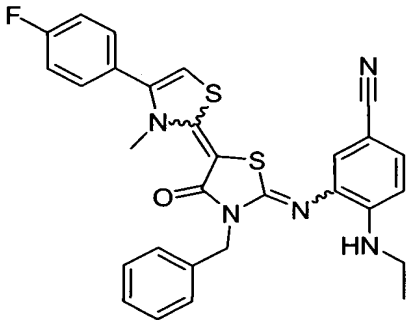
Preparation of 3-[3'-b nzyl-3-methyl-4-(4-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitril



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-nitroacetophenone. MS(ESI): 569 (MH^+).

EXAMPLE 171

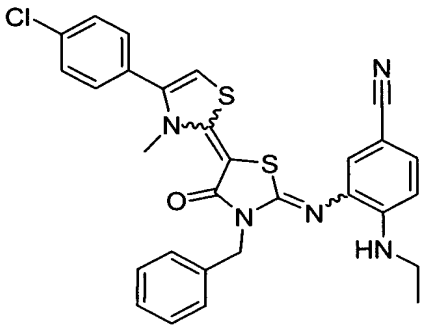
Preparation of 3-[3'-benzyl-4-(4-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-fluoroacetophenone. MS(ESI): 542 (MH^+).

EXAMPLE 172

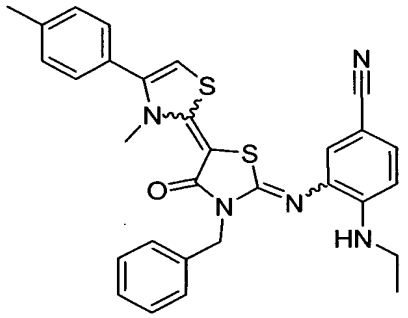
Preparation of 3-[3'-b nzyl-4-(4-chloro-phenyl)-3-methyl-4'- xo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-chloroacetophenone. MS(ESI): 558 (MH^+).

EXAMPLE 173

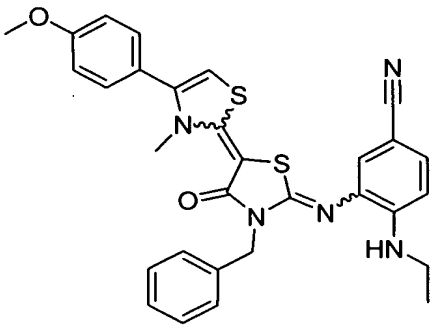
Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4-p-tolyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-methylacetophenone. MS(ESI): 538 (MH^+).

EXAMPLE 174

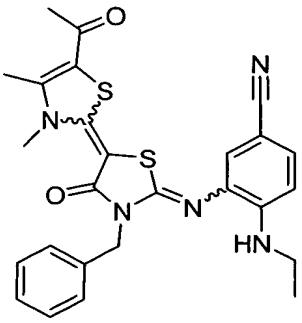
Preparation of 3-[3'-benzyl-4-(4-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-methoxyacetophenone. MS(ESI): 554 (MH^+).

EXAMPLE 175

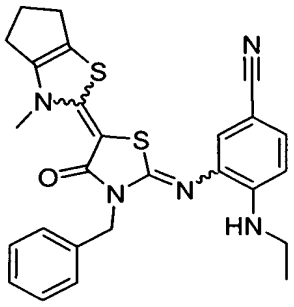
Preparation of 3-(5-acetyl-3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-2,4-pentanedione. MS(ESI): 504 (MH^+).

EXAMPLE 176

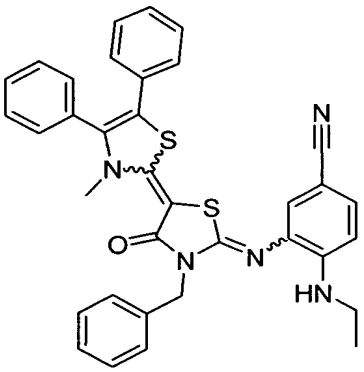
Preparation of 3-[3-benzyl-5-(3-methyl-3,4,5,6-tetrahydrocyclopentathiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chlorocyclopentanone. MS(ESI): 488 (MH^+).

EXAMPLE 177

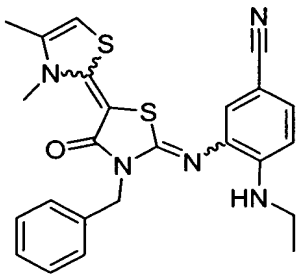
Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4,5-diphenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chloro-2-phenylacetophenone. MS(ESI): 600 (MH^+).

EXAMPLE 178

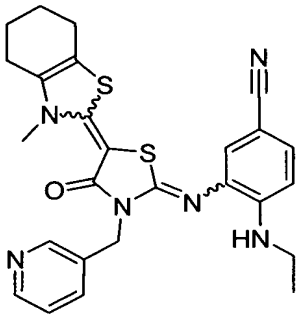
Preparation of 3-(3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with chloroacetone. MS(ESI): 462 (MH^+).

EXAMPLE 179

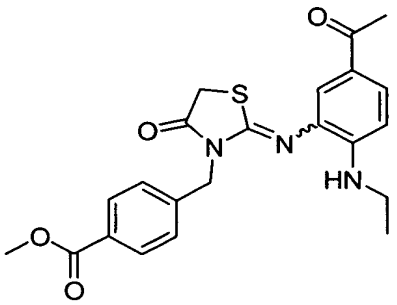
Preparation of 4-ethylamino-3-[5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 4-ethylamino-3-(4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino)benzonitrile. MS(ESI): 503 (MH^+).

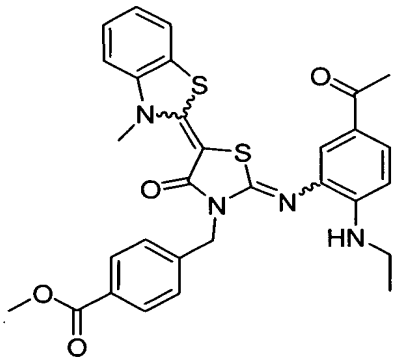
EXAMPLE 180

A. Preparation of methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoate



In a manner similar to Example 52, the title compound was prepared from 3'-amino-4'-ethylaminoacetophenone and methyl 4-(isothiocyantomethyl)benzoate—generated from methyl 4-(aminomethyl)benzoate hydrochloride and thiophosgene. ^{1}H-NMR ($CDCl_3$): δ 8.04 (2H, d), 7.69 (1H, m), 7.58 (1H, s), 7.47 (2H, d), 6.52 (1H, d), 5.10 (2H, s), 3.96 (2H, s), 3.92 (3H, s), 3.05 (2H, q), 2.49 (3H, s), 1.03 (3H, t).

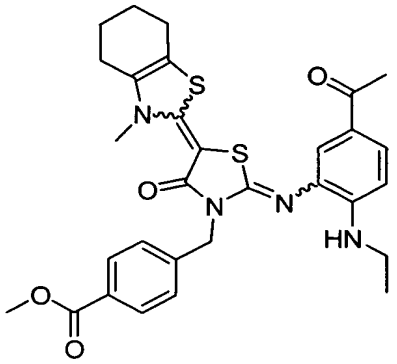
B. Preparation of methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate



The title compound was prepared from intermediate 4-[2-(5-acetyl-2-ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoic acid methyl ester and 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate in a manner similar to Example 45. ^{1}H-NMR ($CDCl_3$): δ 8.03 (2H, d), 7.64-7.70 (2H, m), 7.49-7.55 (3H, m), 7.36 (1H, m), 7.20 (1H, m), 7.08 (1H, d), 6.51 (1H, d), 5.24 (2H, s), 4.15 (1H, br t), 3.91 (3H, s), 3.80 (3H, s), 3.04 (2H, m), 2.51 (3H, s), 1.01 (3H, s); MS(ESI): 573 (MH^+).

EXAMPLE 181

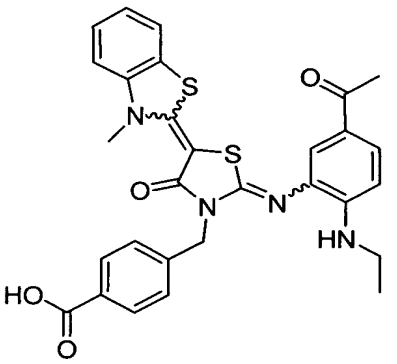
Preparation of methyl 4-[2-(5-acetyl-2-ethylamino-phenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-b nzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate



The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 4-[2-(5-acetyl-2-ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoic acid methyl ester. MS(ESI): 577 (MH^+).

EXAMPLE 182

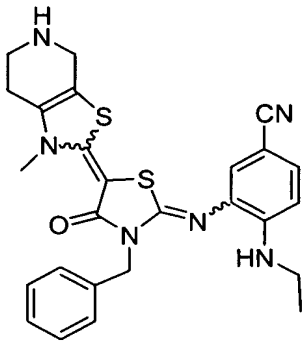
Preparation of 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid



The product of Example 180 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 559 (MH^+).

EXAMPLE 183

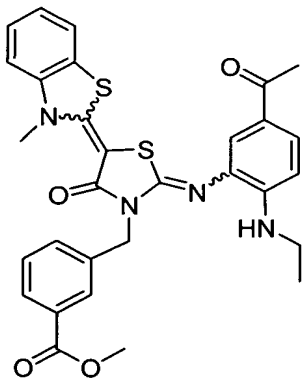
Preparation of 3-[3-benzyl-5-(1-methyl-4,5,6,7-t trahydro-1*H*-thiazolo[5,4-c]pyridin-2-ylidene)-4-oxothiazolidin-2-yliden amino]-4-thylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-bromo-4-oxopiperidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester—synthesized according to a published procedure [*J. Med. Chem.* **1998**, *41*, 1409-1416]. ^{1}H-NMR ($CDCl_3$): δ 7.39-7.43 (2H, m), 7.33 (2H, m), 7.24-7.29 (2H, m), 7.20 (1H, d), 6.47 (1H, d), 5.15 (2H, s), 4.28 (1H, br t), 3.81 (2H, br s), 3.63 (3H, s), 3.22 (2H, br s), 2.99 (2H, q), 2.49 (2H, br s), 1.01 (3H, t); MS(ESI): 503 (MH^+).

EXAMPLE 184

Preparation of methyl 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate



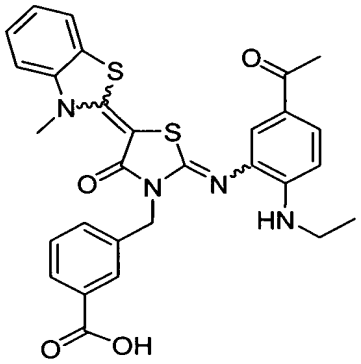
To a solution of methyl 3-(bromomethyl)benzoate (1.0 g, 4.4 mmol) in anhydrous DMF (10 mL) was added sodium azide (285 mg, 4.4 mmol). The resulting mixture was heated at 50°C for 2h, cooled, diluted with $CHCl_3$ (100 mL), washed with water (5 x 50 mL), dried over $MgSO_4$ and concentrated

under reduced pressure to yield methyl 3-(azidomethyl)benzoate (0.84 g, quant.), which was used without purification. ^{1}H-NMR ($CDCl_3$): δ 8.01 (2H, m), 7.44-7.54 (2H, m), 4.42 (2H, s), 3.94 (3H, s).

Methyl 3-(azidomethyl)benzoate was transformed into its amine (Staudinger conditions) and then converted into its isocyanate in a manner similar to Example 45. The title compound then was prepared in a manner similar to that described in Example 180 by replacing methyl 4-(isothiocyantomethyl)benzoate with methyl 3-(isothiocyantomethyl)benzoate. ^{1}H-NMR ($CDCl_3$): δ 8.13 (1H, br s), 7.98 (1H, d), 7.60-7.70 (3H, m), 7.53 (1H, d), 7.43 (1H, m), 7.36 (1H, m), 7.20 (1H, m), 7.07 (1H, d), 6.52 (1H, d), 5.24 (2H, s), 4.20 (1H, br t), 3.90 (3H, s), 3.79 (3H, s), 3.05 (2H, m), 2.51 (3H, s), 1.01 (3H, t); MS(ESI): 573 (MH^+).

EXAMPLE 185

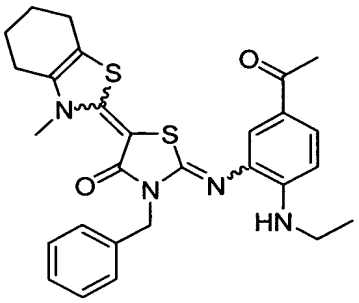
Preparation of 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid



The product of Example 184 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 559 (MH^+).

EXAMPLE 186

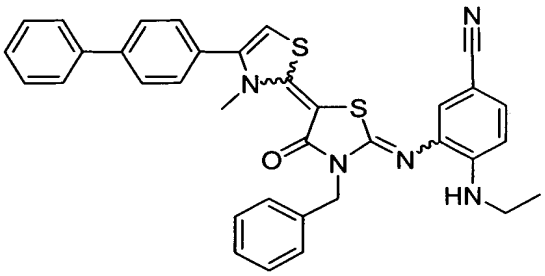
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one. MS(ESI): 519 (MH^+).

EXAMPLE 187

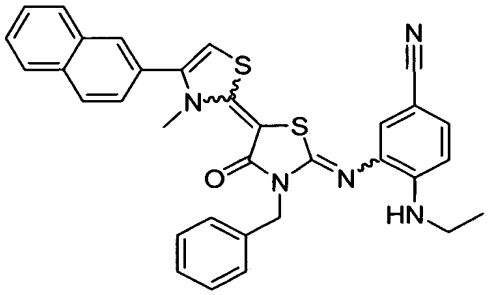
Preparation of 3-(3'-benzyl-4-biphenyl-4-yl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-phenylacetophenone. MS(ESI): 600 (MH^+).

EXAMPLE 188

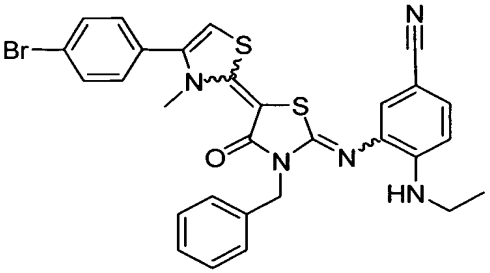
Preparation of 3-(3'-benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-acetonaphthone. MS(ESI): 574 (MH^+).

EXAMPLE 189

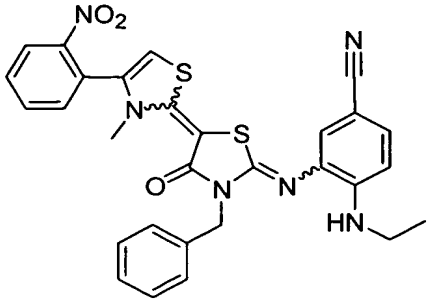
Preparation of 3-[3'-benzyl-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2,4'-dibromoacetophenone. MS(ESI): 602 (MH^+).

EXAMPLE 190

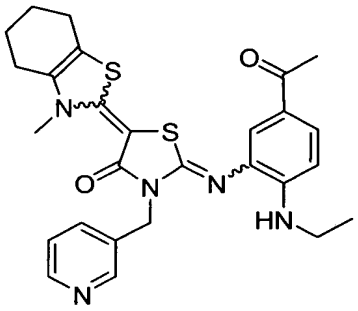
Preparation of 3-[3'-benzyl-3-methyl-4-(2-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-nitroacetophenone. MS(ESI): 569 (MH^+).

EXAMPLE 191

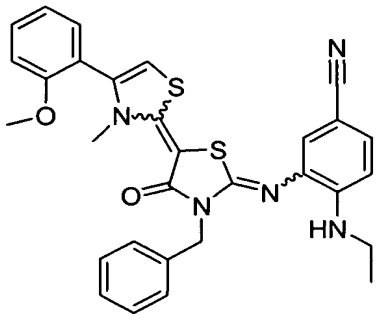
Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one



The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 2-(5-acetyl-2-ethylaminophenylimino)-3-pyridin-3-ylmethyl-thiazolidin-4-one. MS(ESI): 520 (MH^+).

EXAMPLE 192

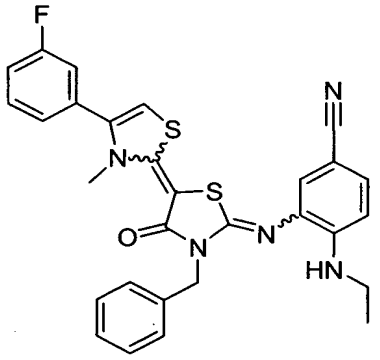
Preparation of 3-[3'-benzyl-4-(2-m thoxyph nyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylid neamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-methoxyacetophenone. MS(ESI): 554 (MH^+).

EXAMPLE 193

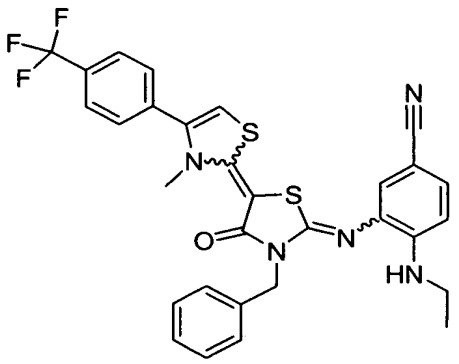
Preparation of 3-[3'-benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-3'-fluoroacetophenone. MS(ESI): 542 (MH^+).

EXAMPLE 194

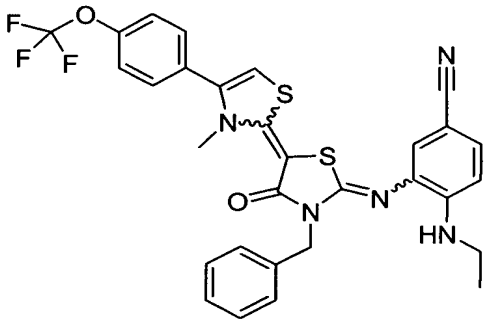
Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethylphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-trifluoromethyl-acetophenone. MS(ESI): 592 (MH^+).

EXAMPLE 195

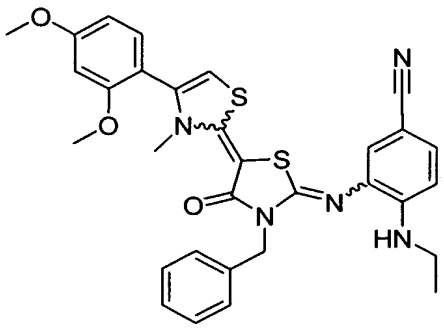
Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethoxyphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-(trifluoromethoxy)acetophenone. MS(ESI): 608 (MH^+).

EXAMPLE 196

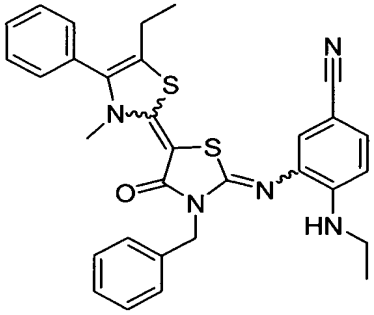
Preparation of 3-[3'-benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2',4'-dimethoxyacetophenone. MS(ESI): 584 (MH^+).

EXAMPLE 197

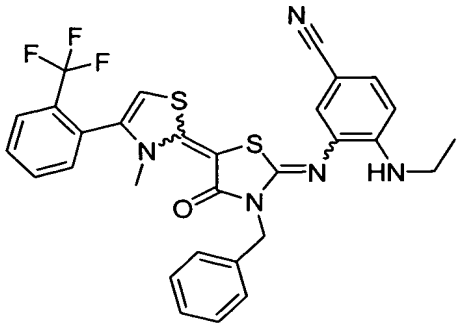
Preparation of 3-(3'-benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromobutyrophenone. MS(ESI): 552 (MH^+).

EXAMPLE 198

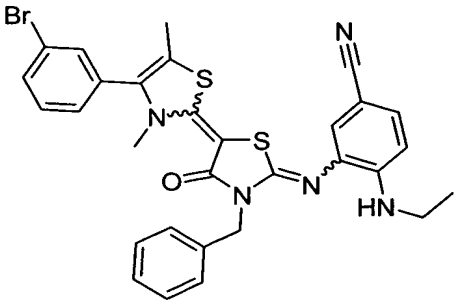
Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(2-trifluoromethylphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-(trifluoromethyl)acetophenone. MS(ESI): 592 (MH^+).

EXAMPLE 199

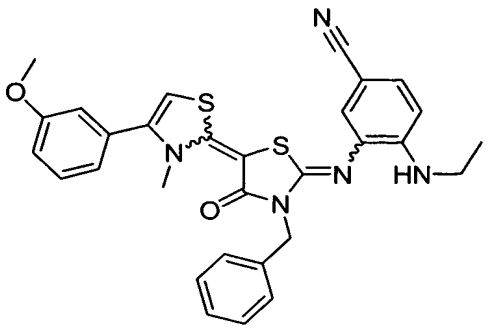
Preparation of 3-[3'-benzyl-4-(3-bromophenyl)-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2,3'-dibromopropiophenone. MS(ESI): 617 (MH^+).

EXAMPLE 200

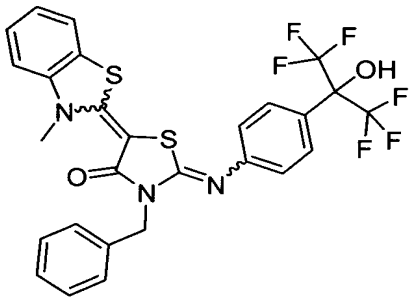
Preparation of 3-[3'-benzyl-4-(3-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-3'-methoxyacetophenone. MS(ESI): 554 (MH^+).

EXAMPLE 201

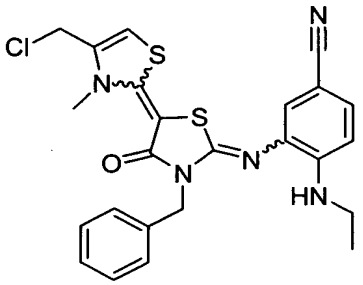
Preparation of 3-benzyl-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 52 by replacing aniline with 4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)aniline. MS(ESI): 596 (MH^+).

EXAMPLE 202

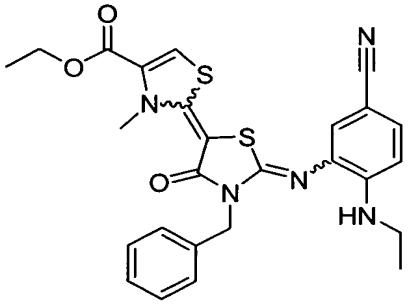
Preparation of 3-(3'-benzyl-4-chlorom thyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1,3-dichloroacetone. MS(ESI): 496 (MH^+).

EXAMPLE 203

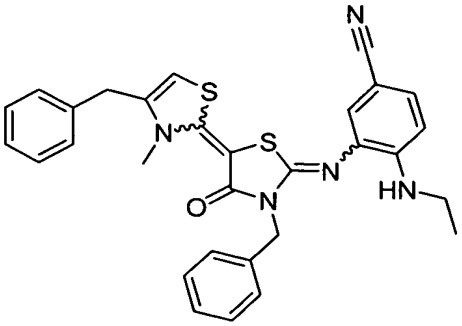
Preparation of 3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid ethyl ester



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with ethyl bromopyruvate. MS(ESI): 520 (MH^+).

EXAMPLE 204

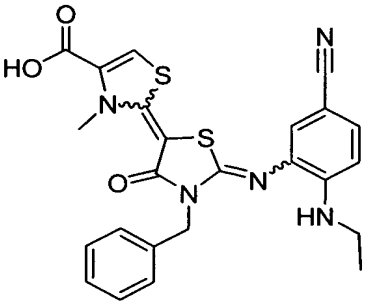
Preparation of 3-(4,3'-dibenzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylid neamino)-4-ethylaminob nzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-chloro-3-phenylpropan-2-one. MS(ESI): 538 (MH^+).

EXAMPLE 205

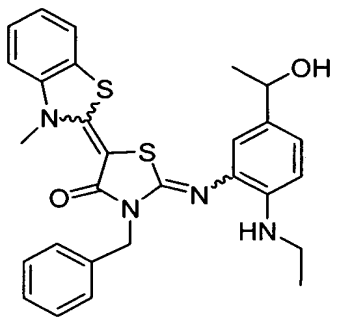
Preparation of 3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid



The product of Example 203 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 492 (MH^+).

EXAMPLE 206

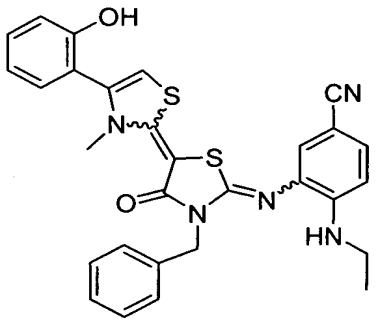
Preparation f 3-benzyl-2-[2-ethylamino-5-(1-hydroxyethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-yliden)thiazolidin-4-one



The product of Example 38 was reduced with sodium borohydride in 1:1 MeOH/THF and chromatographed (TEA-washed silica gel, 0-10% MeOH/DCM) to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.47-7.54 (3H, m), 7.28-7.37 (4H, m), 7.17 (1H, m), 6.99-7.06 (3H, m), 6.57 (1H, d), 5.19 (2H, s), 4.80 (1H, q), 3.76 (3H, s), 3.01 (2H, q), 1.48 (3H, d), 1.04 (3H, s); MS(ESI): 517 (MH^+).

EXAMPLE 207

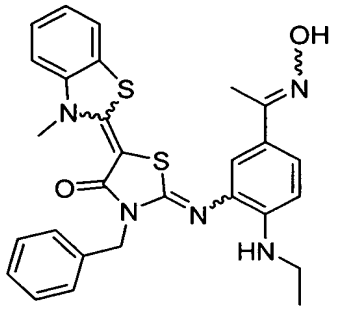
Preparation of 3-[3'-benzyl-4-(2-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The product of Example 192 was treated with boron tribromide in DCM at 25°C. After 15 min the product mixture was quenched with brine, concentrated and chromatographed (silica gel, 0-10% MeOH/DCM) to yield the title compound. MS(ESI): 540 (MH^+).

EXAMPLE 208

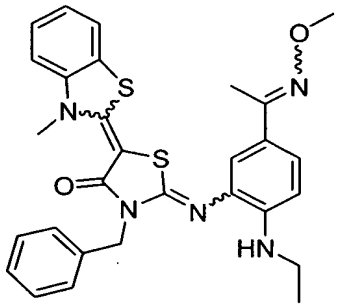
Preparation of 3-benzyl-2-[2-ethylamino-5-(1-hydroxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



To the product of Example 38 was added hydroxylamine hydrochloride (2 equiv) and pyridine. The resulting mixture was heated at 80°C for 24h, cooled, concentrated and chromatographed (TEA-washed silica gel, 0-50% EtOAc/Hex) to give the title compound. ^{1}H-NMR (DMSO-d_6): δ 11.07 (1H, s), 7.88 (1H, s), 7.67 (2H, m), 7.53 (1H, d), 7.39 (2H, m), 7.21-7.33 (5H, m), 7.09-7.14 (1H, m), 5.05 (2H, s). 3.92 (2H, q), 3.27 (3H, s), 2.23 (3H, s), 1.03 (3H, t); MS(ESI): 530 (MH^+).

EXAMPLE 209

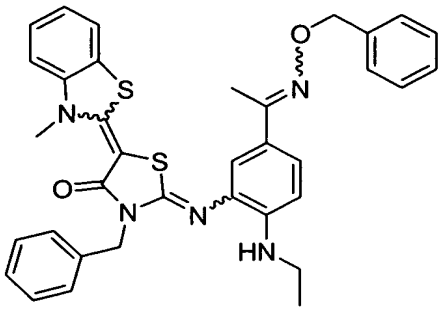
Preparation of 3-benzyl-2-[2-ethylamino-5-(1-methoxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with *O*-methylhydroxylamine hydrochloride. MS(ESI): 544 (MH^+).

EXAMPLE 210

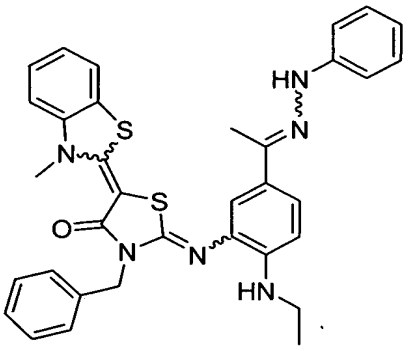
Preparation of 3-benzyl-2-[5-(1-benzyloxyiminoethyl)-2-ethylaminophenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with *O*-benzylhydroxylamine hydrochloride. MS(ESI): 620 (MH^+).

EXAMPLE 211

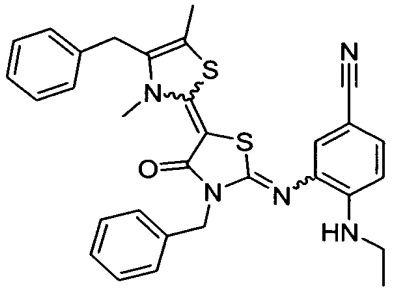
Preparation of 3-benzyl-2-{2-ethylamino-5-[1-(phenylhydrazono)ethyl]-phenylimino}-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with phenylhydrazine. MS(ESI): 605 (MH^+).

EXAMPLE 212

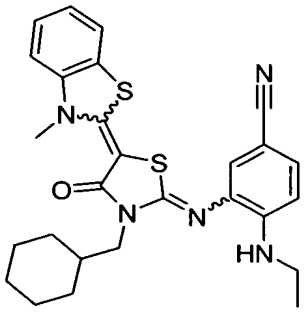
Preparation of 3-(4,3'-dib nzyl-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylid neamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-1-phenylbutan-2-one. MS(ESI): 552 (MH^+).

EXAMPLE 213

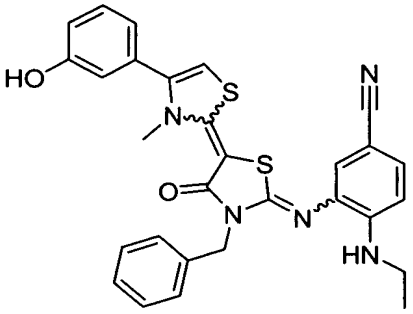
Preparation of 3-[3-cyclohexylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with cyclohexylmethyl isothiocyanate. MS(ESI): 504 (MH^+).

EXAMPLE 214

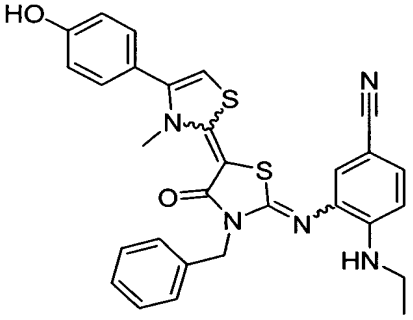
Preparation of 3-[3'-benzyl-4-(3-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolylid n-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 200 in a manner similar to that described in Example 207. MS(ESI): 540 (MH^+).

EXAMPLE 215

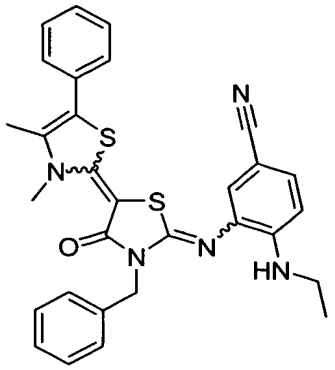
Preparation of 3-[3'-benzyl-4-(4-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 174 in a manner similar to that described in Example 207. MS(ESI): 540 (MH^+).

EXAMPLE 216

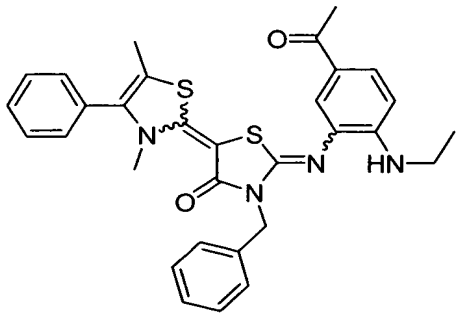
Preparation of 3-(3'-benzyl-3,4-dimethyl-4'-oxo-5-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminob nzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-chloro-1-phenylpropan-2-one—generated in situ by addition of methylmagnesium chloride to chlorophenylacetyl chloride (-78 to 25°C). MS(ESI): 538 (MH^+).

EXAMPLE 217

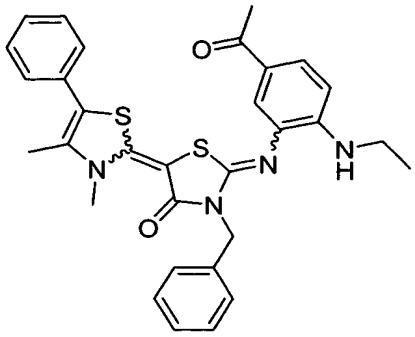
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,5-dimethyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 52 by replacing 3-amino-4-ethylaminobenzonitrile with 3'amino-4'-ethylaminoacetophenone. MS(ESI): 555 (MH^+).

EXAMPLE 218

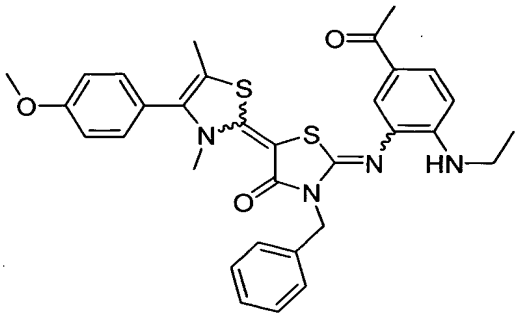
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,4-dimethyl-5-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-on



The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 1-chloro-1-phenylpropan-2-one. MS(ESI): 555 (MH^+).

EXAMPLE 219

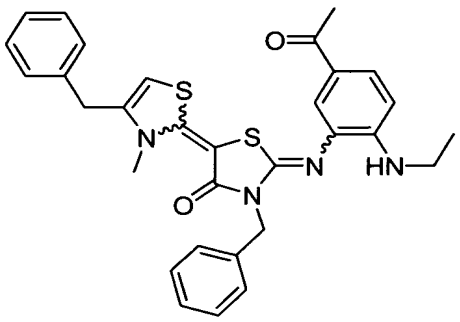
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(4-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-4'-methoxypropiophenone. MS(ESI): 585 (MH^+).

EXAMPLE 220

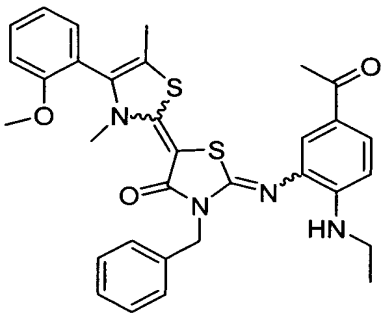
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-4,3'-dibenzyl-3-m thyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-on



The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 1-chloro-3-phenylpropan-2-one. MS(ESI): 555 (MH^+).

EXAMPLE 221

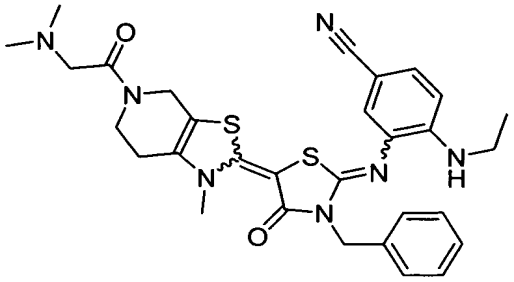
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(2-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-2'-methoxypropiophenone. MS(ESI): 585 (MH^+).

EXAMPLE 222

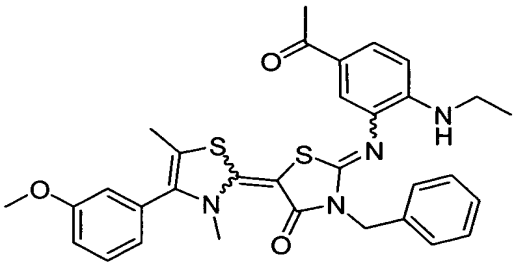
Preparation of 3-{3-benzyl-5-[5-(2-dimethylaminoacetyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-thiazolo[5,4-c]pyridin-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



To the product of Example 183 in $CHCl_3$ was added *N,N*-dimethylaminoacetyl chloride and TEA. After 4h the product mixture was concentrated and chromatographed (silica gel, 0-40% EtOAc/Hex) to yield the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.39-7.44 (2H, m), 7.33 (2H, m), 7.23-7.30 (2H m), 7.19 (1H, br s), 6.47 (1H, d), 5.15 (2H, s), 4.61 (1H, br s), 4.51 (1H, br s), 4.27 (1H, m), 3.92 (2H, m), 3.64 (3H, br s), 3.22 (1H, br s), 3.16 (1H, br s), 2.99 (2H, m), 2.63 (1H, br s), 2.56 (1H, br s), 2.31 (3H, s), 2.28 (3H, s), 1.01 (3H, t); MS(ESI): 588 (MH^+).

EXAMPLE 223

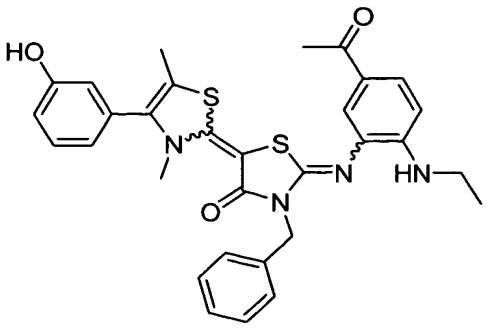
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-3'-methoxypropiophenone. MS(ESI): 585 (MH^+).

EXAMPLE 224

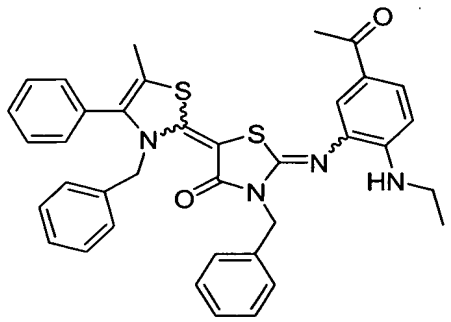
Preparation of 2'-(5-ac tyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-hydroxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared from the product of Example 223 in a manner similar to that described in Example 207. MS(ESI): 571 (MH^+).

EXAMPLE 225

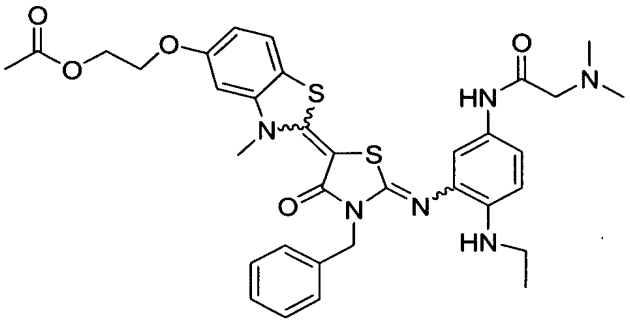
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3,3'-dibenzyl-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium benzyldithiocarbamate—generated from benzylamine, carbon disulfide and TEA. MS(ESI): 631 (MH^+).

EXAMPLE 226

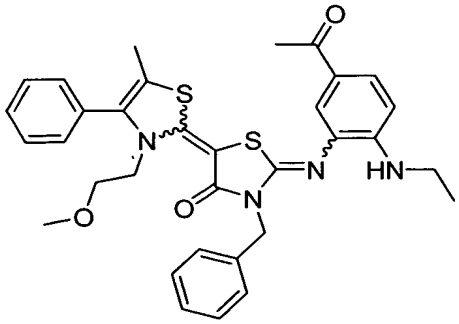
Preparation of N-(3-{3-benzyl-5-[5-(2-acetoxy thoxy)-3-methyl-3*H*-benzothiazol-2-ylid ne]-4-oxothiazolidin-2-ylid neamino}-4-ethylaminophenyl)-2-dimethylamino-acetamide



To the product of Example 145 (21 mg, 32 μmol) in acetone (2 mL) was added tetra-*n*-butylammonium iodide (24 mg, 65 μmol). The solution was stirred at 40°C for 17h prior to the addition of sodium acetate (50 mg, 0.64 mmol). The reaction solution was heated at 75°C for 48h. After cooling the solution was diluted with EtOAc (25 mL), washed with saturated $NaHCO_3$ (20 mL) and water (2 x 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude sample was chromatographed (silica gel, DCM) to provide the title compound (7 mg, 33%). ^{1}H-NMR ($CDCl_3$) δ 7.87 (1H, s), 7.60 (1H, dd), 7.30-7.35 (3H, m), 7.17-7.22 (3H, m), 6.60 (1H, dd), 6.48 (1H, d), 5.27 (2H, s), 4.72 (1H, s), 4.39 (2H, t), 4.16 (2H, t), 3.69 (2H, q), 3.16 (2H, s), 3.08 (3H, s), 2.43 (6H, s), 2.06 (3H, s), 0.91 (3H, t); MS(ESI): 675 (MH^+).

EXAMPLE 227

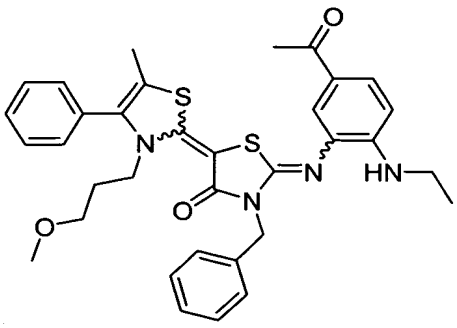
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-methoxyethyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 2-methoxyethyldithiocarbamate—generated from 2-methoxy-ethylamine, carbon disulfide and TEA. MS(ESI): 599 (MH^+).

EXAMPLE 228

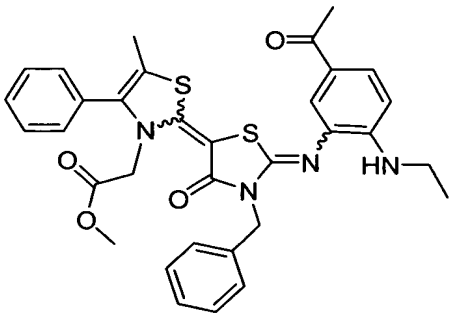
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(3-methoxypropyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 3-methoxypropyldithiocarbamate—generated from 2-methoxy-propylamine, carbon disulfide and TEA. MS(ESI): 613 (MH^+).

EXAMPLE 229

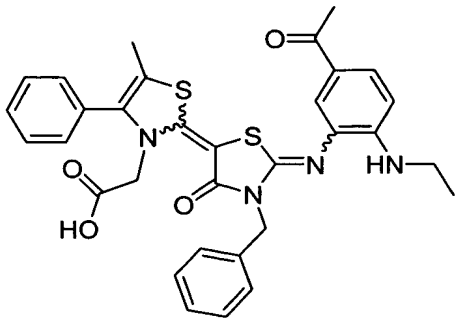
Preparation of [2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5']bithiazolyliden-3-yl]acetic acid methyl ester



The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium methoxycarbonylmethyldithiocarbamate—generated from glycine methyl ester, carbon disulfide and TEA. MS(ESI): 613 (MH^+).

EXAMPLE 230

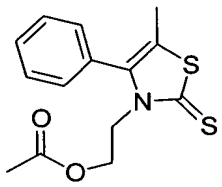
Preparation of [2'-(5-ac tyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-ph nyl-3',4'-dihydro-2'*H*-[2,5']bithiazolyliden-3-yl]ac tic acid



The product of Example 229 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 599 (MH^+).

EXAMPLE 231

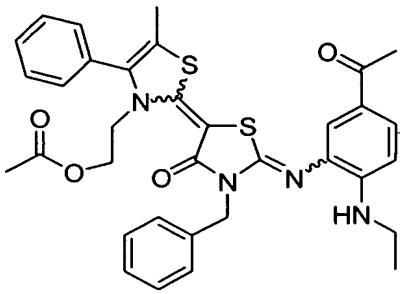
A. Preparation of 2-(5-methyl-4-phenyl-2-thioxothiazol-3-yl)ethyl acetate



3-(2-Hydroxyethyl)-5-methyl-4-phenyl-3*H*-thiazole-2-thione was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 2-hydroxyethyldithiocarbamate—generated from ethanolamine, carbon disulfide and TEA.

Intermediate 3-(2-hydroxyethyl)-5-methyl-4-phenyl-3*H*-thiazole-2-thione was treated with acetic anhydride (1 equiv) and TEA (2 equiv) in $CHCl_3$. After 12h the product mixture was concentrated and chromatographed (silica gel, 0-40% EtOAc/Hex) to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.50-7.55 (3H, m), 7.28-7.32 (2H, m), 4.32 (2H, t), 4.26 (2H, t), 2.03 (3H, s), 1.93 (3H, s).

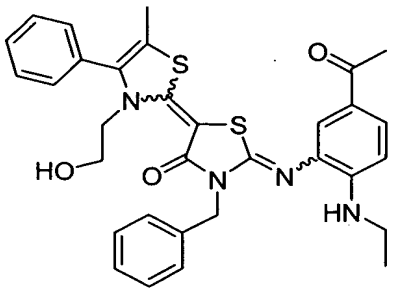
B. Preparation of 2-[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5']bithiazolyliden-3-yl]ethyl acetate



In a manner similar to that described in Example 52, intermediate 2-(5-methyl-4-phenyl-2-thioxothiazol-3-yl)ethyl acetate was alkylated with methyl *p*-toluenesulfonate and condensed with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one to yield the title compound. ^{1}H-NMR ($CDCl_3$): δ 7.63-7.67 (2H, m), 7.44-7.51 (5H, m), 7.28-7.37 (5H, m), 6.50 (1H, d), 5.19 (2H, s), 4.30 (1H, br t), 4.03 (4H, m), 3.06 (2H, m), 2.48 (3H, s), 2.05 (3H, s), 1.89 (3H, s), 1.05 (3H, t); MS(ESI): 627 (MH^+).

EXAMPLE 232

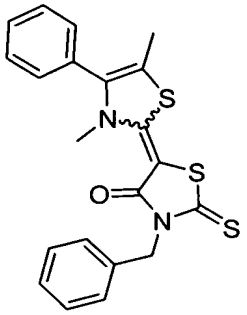
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-hydroxyethyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The product of Example 231 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 585 (MH^+).

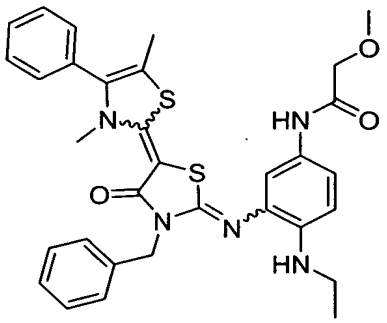
EXAMPLE 233

A. Preparation of 3'-benzyl-3,5-dimethyl-4-phenyl-2'-thioxo-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-methylthiobenzothiazole with 3,5-dimethyl-4-phenyl-3*H*-thiazole-2-thione. ^{1}H-NMR ($CDCl_3$): δ 7.50-7.58 (5H, m), 7.23-7.32 (5H, m), 5.39 (2H, s), 3.54 (3H, s), 2.11 (3H, s).

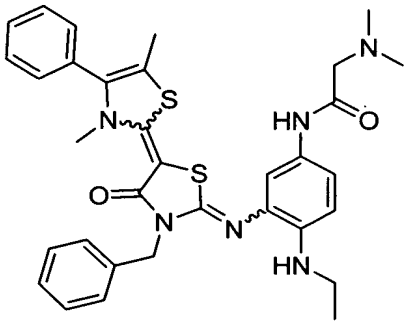
B. Preparation of N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-methoxyacetamide



Likewise as described in Example 1, intermediate 3'-benzyl-3,5-dimethyl-4-phenyl-2'-thioxo-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one was alkylated with methyl *p*-toluenesulfonate and condensed with *N*-(3-amino-4-ethylaminophenyl)-2-methoxyacetamide to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.00 (1H, br s), 7.42-7.51 (5H, m), 7.30-7.37 (3H, m), 7.19-7.26 (3H, m). 7.11 (1H, d), 6.53 (1H, br s), 5.18 (2H, s), 3.97 (2H, s), 3.47 (3H, s), 3.42 (3H, s), 2.98 (2H, m), 2.06 (3H, s), 1.02 (3H, br t); MS(ESI): 600 (MH^+).

EXAMPLE 234

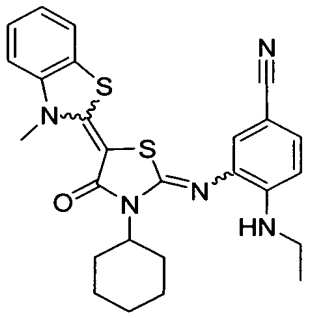
Preparation of N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-dimethylaminoacetamide



The title compound was prepared in a manner similar to that described in Example 233 by replacing *N*-(3-amino-4-ethylaminophenyl)-2-methoxyacetamide with *N*-(3-amino-4-ethylaminophenyl)-2-dimethylaminoacetamide. MS(ESI): 613 (MH^+).

EXAMPLE 235

Preparation of 3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



To a biphasic mixture of cyclohexylamine (2.3 mL, 20 mmol) in $CHCl_3$ (60 mL) and saturated aqueous $NaHCO_3$ (40 mL) was added a solution of $CSCl_2$ (1.57 mL, 20 mmol) in $CHCl_3$ (5 mL) dropwise at 5°C. The mixture was stirred 1h at 5°C. Methyl thioglycolate (1.9 mL, 20 mmol) was added, and the mixture was stirred overnight at 20°C. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with water, 1N HCl, water, saturated aqueous $NaHCO_3$ and then

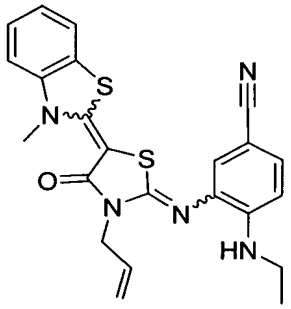
dried over $MgSO_4$. Evaporation of solvent under reduced pressure gave a crude material, which was used in the next step without purification.

To a solution of the above product in toluene (80 mL) was added TsOH (100 mg), and the mixture was heated at reflux for 8h with a dropping funnel containing 4Å molecular sieves attached to the flask. After cooling, solid was removed by filtration. Evaporation of the filtrate gave a crude, which was purified by column chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 3:7) to afford 3-cyclohexylrhodanine (1.24 g). ^{1}H-NMR ($CDCl_3$): δ 4.86 (1H, m), 3.82 (2H, s), 2.30 (2H, q), 1.86 (2H, m), 1.58-1.72 (3H, m), 1.16-1.42 (3H, m).

The title compound was prepared in a manner similar to that described in Example 32 by replacing 3-benzylrhodanine with 3-cyclohexylrhodanine. MS(ESI): 490 (MH^+).

EXAMPLE 236

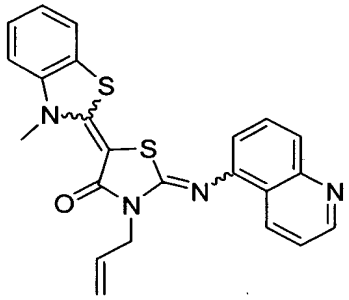
Preparation of 3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with allylamine. MS(ESI): 448 (MH^+).

EXAMPLE 237

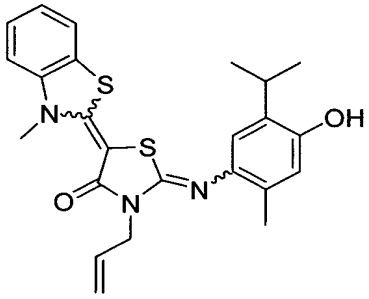
Preparation of 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 5-aminoquinoline. MS(ESI): 431 (MH^+).

EXAMPLE 238

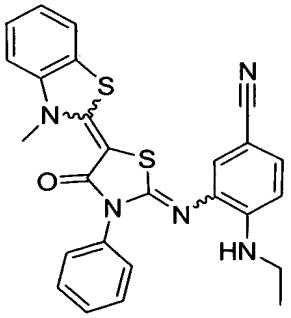
Preparation of 3-allyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 4-aminothymol hydrochloride. MS(ESI): 452 (MH^+).

EXAMPLE 239

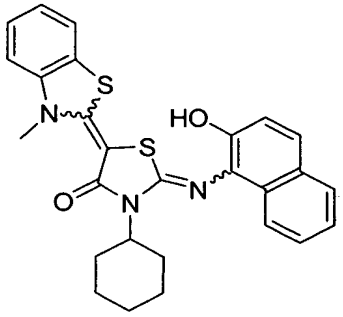
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with aniline. MS(ESI): 484 (MH^+).

EXAMPLE 240

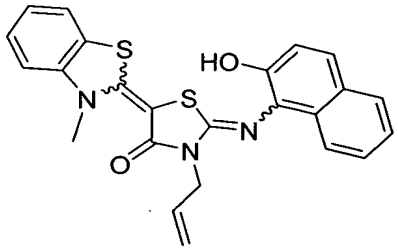
Preparation of 3-cyclohexyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 235 by replacing 3-amino-4-ethylaminobenzonitrile with 1-amino-2-naphthol hydrochloride. MS(ESI): 488 (MH^+).

EXAMPLE 241

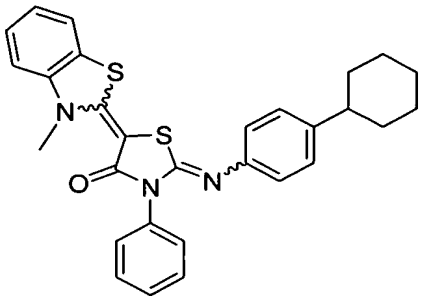
Preparation of 3-allyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 1-amino-2-naphthol hydrochloride. MS(ESI): 446 (MH^+).

EXAMPLE 242

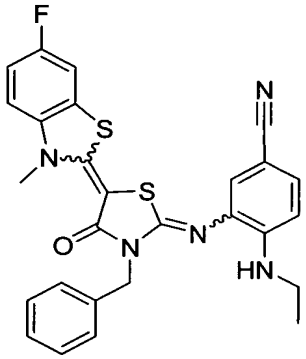
Preparation of 2-(4-cyclohexylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-phenylthiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 239 by replacing 3-amino-4-ethylaminobenzonitrile with 4-cyclohexylaniline. MS(ESI): 498 (MH^+).

EXAMPLE 243

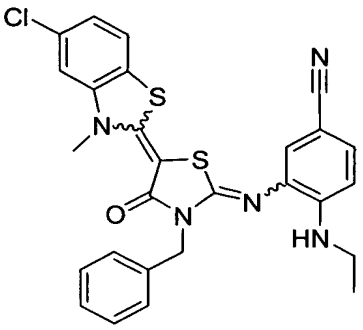
Preparation of 3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 6-fluoro-2-mercaptobenzothiazole. MS(ESI): 516 (MH^+).

EXAMPLE 244

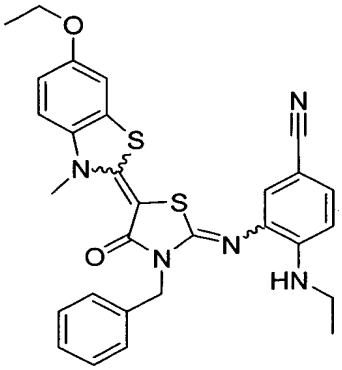
Preparation of 3-[3-benzyl-5-(5-chloro-3-methyl-3*H*-b nzothiazol-2-ylid ne)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 5-chloro-2-mercaptobenzothiazole. MS(ESI): 532 (MH^+).

EXAMPLE 245

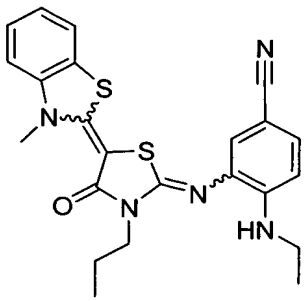
Preparation of 3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 6-ethoxy-2-mercaptobenzothiazole. MS(ESI): 542 (MH^+).

EXAMPLE 246

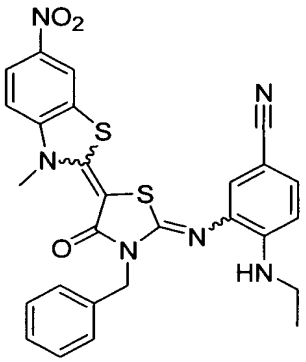
Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylid ne)-4-oxo-3-propylthiazolidin-2-ylideneamino]benzonitrile



The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with propylamine. MS(ESI): 450 (MH^+).

EXAMPLE 247

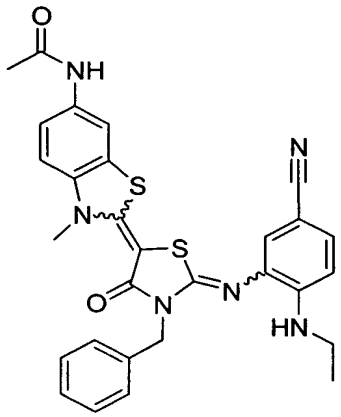
Preparation of 3-[3-benzyl-5-(3-methyl-6-nitro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 2-mercapto-6-nitrobenzothiazole. MS(ESI): 543 (MH^+).

EXAMPLE 248

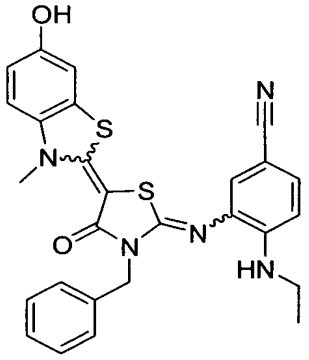
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-yliden]-3-methyl-2,3-dihydrobenzothiazol-6-yl}acetamide



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 2-mercapto-6-acetamidobenzothiazole. MS(ESI): 555 (MH^+).

EXAMPLE 249

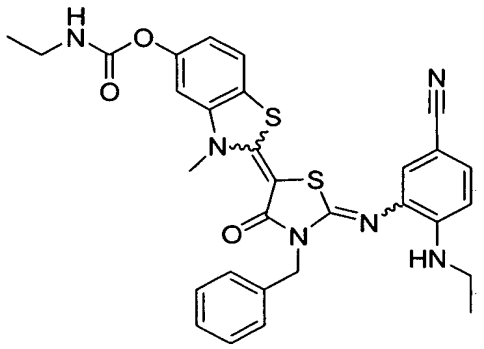
Preparation of 3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 245 in a manner similar to that described in Example 57. MS(ESI): 514 (MH^+).

EXAMPLE 250

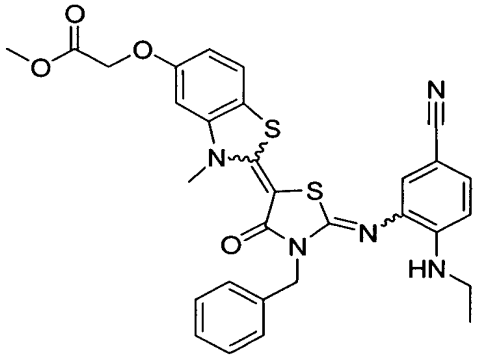
Preparation of ethylcarbamic acid 2-[3-b nzyl-2-(5-cyano-2-ethylaminoph nylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiaz l-5-yl ester



The title compound was prepared in a manner similar to that described in Example 58 by replacing dimethylcarbamoyl chloride with ethyl isocyanate. MS(ESI): 585 (MH^+).

EXAMPLE 251

Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid methyl ester

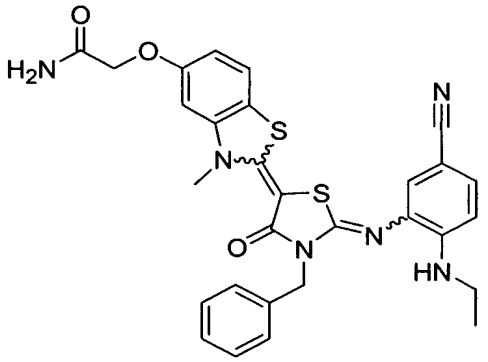


To a suspension of K_2CO_3 (41 mg, 5 equiv) in 2-butanone (2 mL) were added the product of Example 57 (31 mg, 0.06 mmol) and methyl 2-bromoacetate (7 μL, 1.2 equiv). The resulting suspension was heated at 75°C overnight. After cooling, the reaction mixture was filtered, and the filtrate was evaporated to give a crude material, which was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 3:97) to give the title compound (5 mg). ^{1}H-NMR ($CDCl_3$): δ 7.63 (1H, d), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.08 (1H, d), 6.84 (1H, dd), 6.62 (1H, d), 5.13 (2H, s), 4.98 (1H, t),

4.88 (2H, s), 3.79 (3H, s), 3.68 (3H, s), 3.05 (2H, m), 0.99 (3H, t); MS(ESI): 586 (MH^+).

EXAMPLE 252

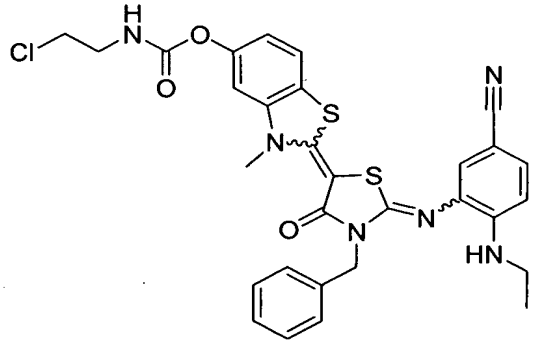
Preparation of 2-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetamide



The title compound was prepared in a manner similar to that described in Example 251 by replacing methyl 2-bromoacetate with 2-bromoacetamide. MS(ESI): 571 (MH^+).

EXAMPLE 253

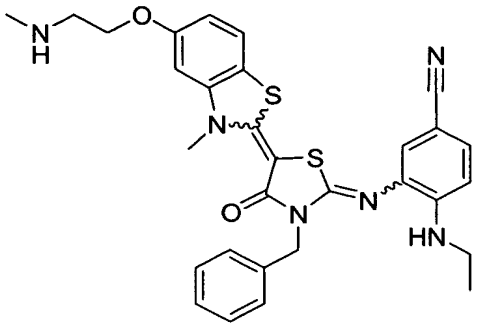
Preparation of (2-chloroethyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester



The title compound was prepared in a manner similar to that described in Example 250 by replacing ethyl isocyanate with 2-chloroethylisocyanate. MS(ESI): 619 (MH^+).

EXAMPLE 254

Preparation of 3-{3-benzyl-5-[3-methyl-5-(2-methylaminoethoxy)-3*H*-benzothiazol-2-ylid ne]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitril

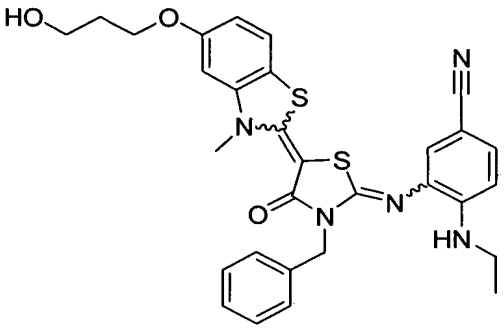


To the product of Example 57 (62 mg, 0.12 mmol) in anhydrous DMF (2 mL) were added 1,2-dibromoethane (100 mL, 10 equiv) and anhydrous K_2CO_3 (166 mg, 10 equiv). The suspension was shaken overnight at 60°C in a sealed tube. After cooling, the reaction mixture was concentrated under reduced pressure, diluted with DCM and acetone, and filtered. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel, eluting with MeOH-DCM (1:19) to give a yellow solid, which was used in the next step without further purification.

The above material was dissolved in 2M solution of methylamine in THF (3 mL) and the solution was heated in a sealed tube for 40h at 60°C. After cooling, the product mixture was concentrated to give a residue, which was purified by chromatography on silica gel, eluting with MeOH-DCM (1:19 to 1:9) to give the title compound (10 mg). ^{1}H-NMR ($CDCl_3$): δ 7.63 (1H, d), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.03 (1H, d), 6.85 (1H, dd), 6.62 (1H, d), 5.13 (2H, s), 4.98 (1H, t), 4.12 (2H, t), 3.79 (3H, s), 3.05 (3H, m), 2.93 (2H, t), 2.3 (3H, s), 0.99 (3H, t); MS(ESI): 571 (MH^+).

EXAMPLE 255

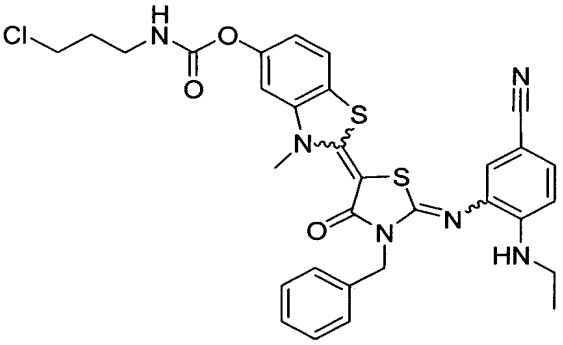
Preparati n of 3-{3-benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylid neamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 59 by replacing 2-bromoethanol with 3-bromopropanol. MS(ESI): 572 (MH^+).

EXAMPLE 256

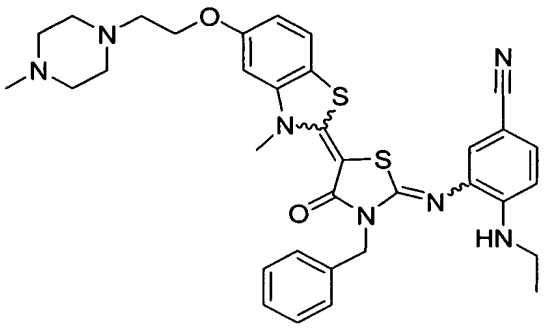
Preparation of (3-chloropropyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester



The title compound was prepared in a manner similar to that described in Example 250 by replacing ethyl isocyanate with 3-chloropropylisocyanate. MS(ESI): 633 (MH^+).

EXAMPLE 257

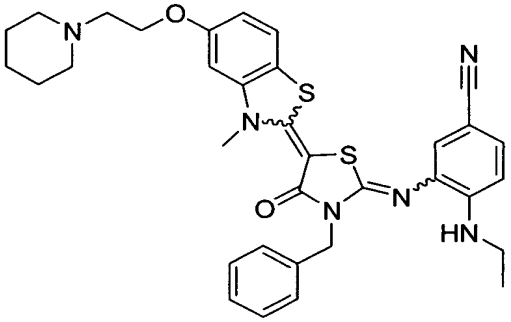
Preparation of 3-(3-benzyl-5-{3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3*H*-benzothiazol-2-ylidene}-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with 1-methylpiperizine. MS(ESI): 640 (MH^+).

EXAMPLE 258

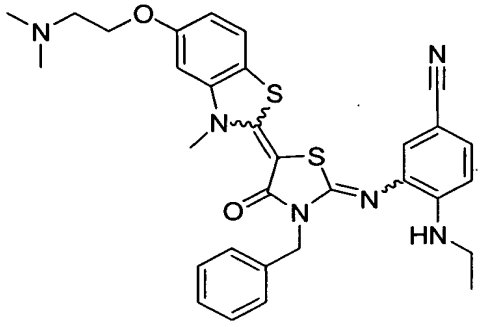
Preparation of 3-{3-benzyl-5-[3-methyl-5-(2-piperidin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with piperidine. MS(ESI): 625 (MH^+).

EXAMPLE 259

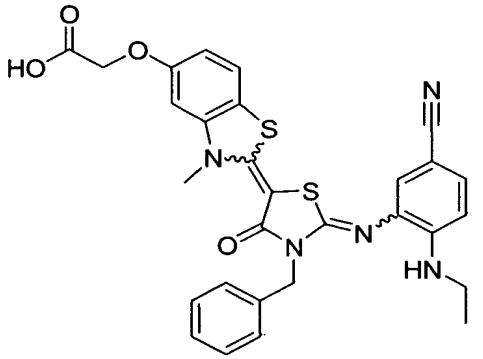
Preparation of 3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with dimethylamine. ^{1}H-NMR ($CDCl_3$): δ 7.43 (2H, m), 7.33 (1H, d), 7.29 (2H, m), 7.25-7.27 (5H, m), 7.20 (1H, d), 6.80 (1H, dd), 6.70 (1H, d), 6.49 (1H, d), 5.18 (2H, s), 4.22 (1H, t), 4.11 (2H, t), 3.77 (3H, s), 3.00 (2H, m), 2.75 (2H, t), 2.35 (6H, s), 1.02 (3H, t), MS(ESI): 585 (MH^+).

EXAMPLE 260

Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid



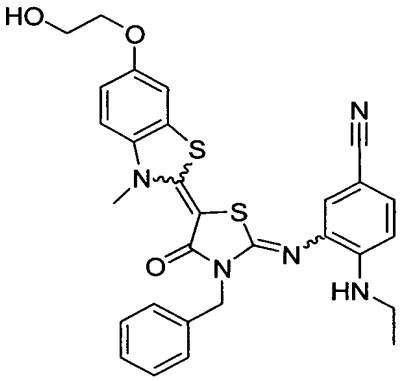
To the product of Example 57 (158 mg, 0.31 mmol) in anhydrous DMF (5 mL) were added *tert*-butyl bromoacetate (460 μL, 10 equiv) and anhydrous K_2CO_3 (425 mg, 10 equiv). The suspension was heated at 80°C under nitrogen for 16h. After cooling, resulting solids were removed by filtration. The filtrate was concentrated to give a residue, which was purified by

chromatography on silica gel, eluting with MeOH-DCM (5:95) to give the product, which was used in the next step without further purification.

The above product was dissolved in a 1:1 mixture of TFA/DCM (2 mL) and the solution was stirred for 1h at 20°C. Evaporation of solvent gave a residue, which was purified by chromatography on silica gel, eluting with MeOH-DCM (5:95) to give the title compound (35 mg, 75%). ^{1}H-NMR ($CDCl_3$): δ 7.61 (1H, m), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.05 (1H, d), 6.82 (1H, dd), 6.62 (1H, d), 5.14 (2H, s), 4.95 (1H, t), 4.76 (2H, t), 3.79 (3H, s), 3.05 (2H, m), 0.99 (3H, t), MS(ESI): 572 (MH^+).

EXAMPLE 261

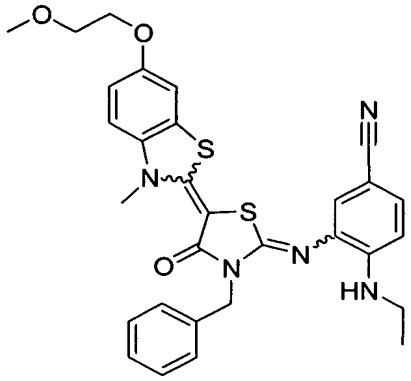
Preparation of 3-{3-benzyl-5-[6-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 59 by replacing the product of Example 57 with the product of Example 249. MS(ESI): 558 (MH^+).

EXAMPLE 262

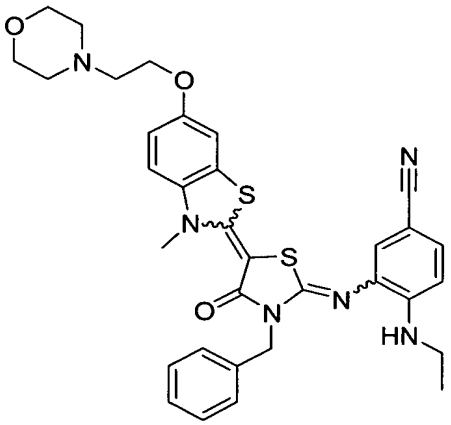
Preparation of 3-{3-benzyl-5-[6-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-yliden]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitril



The title compound was prepared in the same manner as described in Example 261 in the presence of excess methyl *p*-toluenesulfonate. MS(ESI): 572 (MH^+).

EXAMPLE 263

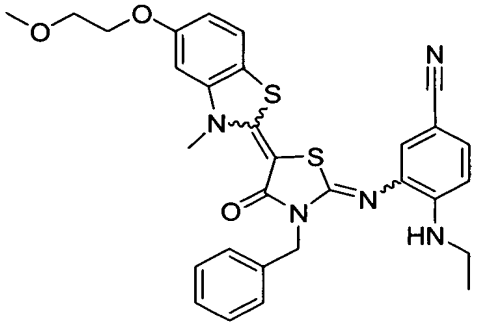
Preparation of 3-{3-benzyl-5-[3-methyl-6-(2-morpholin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 60 by replacing the product of Example 60 with the product of Example 261. MS(ESI): 627 (MH^+).

EXAMPLE 264

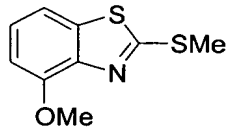
Preparation of 3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in the same manner as described in Example 59 in the presence of excess methyl *p*-toluenesulfonate. MS(ESI): 572 (MH^+).

EXAMPLE 265

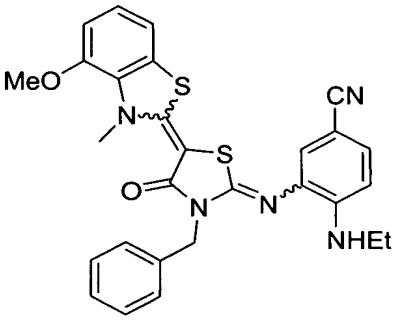
A. Preparation of 4-methoxy-2-methylthiobenzothiazole



2-Amino-4-methoxybenzothiazole (3.6 g, 20 mmol) was dissolved in warm H_3PO_4 (120 mL). The resulting homogeneous solution was cooled to –8°C, and a solution of $NaNO_2$ (8.28 g, 120 mmol) in H_2O (50 mL) was added dropwise with stirring such that the temperature was not allowed to rise above –4°C. The resulting dark-red syrup was added slowly to H_3PO_2 (50% in H_2O, 60 mL) at 0°C with stirring. After the addition was complete, the mixture was allowed to warm to ambient temperature until gas evolution had ceased. The solution was diluted with ice-water, cautiously neutralized with solid Na_2CO_3, and extracted with $CHCl_3$ (3 x 200 mL). The combined extracts were washed with water (2 x 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a red solid (2.87g), which was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 30:70) to yield 4-methoxybenzothiazole (2.14 g, 65%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.90 (1H, s), 7.52 (1H, d), 7.38 (1H, t), 6.93 (1H, d), 4.06 (3H, s).

To a solution of 4-methoxybenzothiazole (495 mg, 3.0 mmol) in anhydrous THF (12 mL) at –78°C was added BuLi (2.5 mL, 1.6M in hexanes, 4.0 mmol) dropwise. The resulting red solution was stirred at –78°C for 2h under N_2. Methyl disulfide (0.55 mL, 6.0 mmol) was added dropwise at –78°C and the mixture was allowed to warm to ambient temperature overnight. The reaction mixture was combined with water and then extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound as a yellow oil (632 mg, 100%), which solidified upon standing and was used without purification. ^{1}H-NMR ($CDCl_3$): δ 7.35 (1H, d), 7.24 (1H, q), 6.86 (1H, d), 4.06 (3H, s), 2.79 (3H, s).

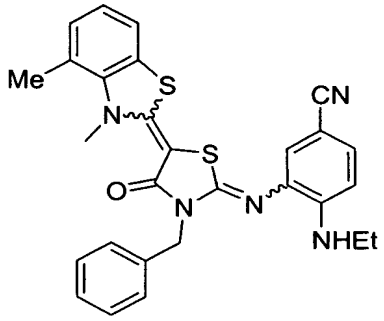
B. Preparation of 3-{3-benzyl-5-[3-methyl-4-methoxy-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



To a suspension of the 4-methoxy2-methylthiobenzothiazole (0.60 g, 2.8 mmol) in anhydrous anisole (8 mL) was added methyl *p*-toluenesulfonate (1.4 mL, 9.0 mmol) and the suspension was heated at 130°C for 3.5 h. After cooling to 20°C, MeCN (5 mL), 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile (119 mg, 0.34 mmol) and TEA (2.0 mL, 14 mmol) were added. The suspension was stirred for 5h at 80°C. After cooling to ambient temperature, yellow solids were collected by filtration, washed with MeCN and dried under high vacuum to afford the title compound (123 mg, 69%). ^{1}H-NMR ($CDCl_3$): δ 7.45-7.11 (9H, m), 6.88-6.85 (1H, m), 6.48 (1H, d), 5.17 (2H, s), 4.08 (3H, s), 3.92 (3H, s), 3.02-2.97 (2H, m), 1.02 (3H, t); MS (ESI): 528 (MH^+).

EXAMPLE 266

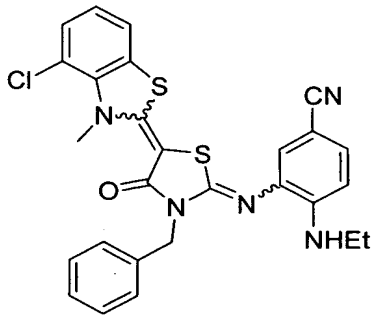
Preparation of 3-{3-b nzyl-5-[3-methyl-4-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-4-methylbenzothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.46-7.06 (10H, m), 6.49 (1H, d), 5.17 (2H, s), 3.88 (3H, s), 3.04-2.97 (2H, m), 2.62 (3H, s), 1.03 (3H, t); MS (ESI): 512 (MH^+).

EXAMPLE 267

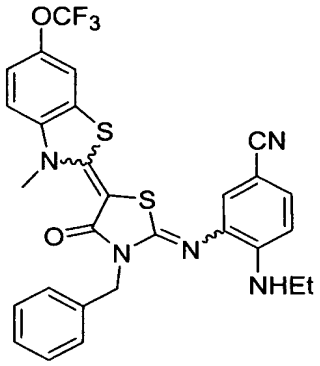
Preparation of 3-{3-benzyl-5-[3-methyl-4-chloro-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-4-chlorobenzothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.45-7.08 (10H, m), 6.50 (1H, d), 5.17 (2H, s), 4.01 (3H, s), 3.04-2.98 (2H, m), 1.03 (3H, t); MS(ESI): 532 (MH^+).

EXAMPLE 268

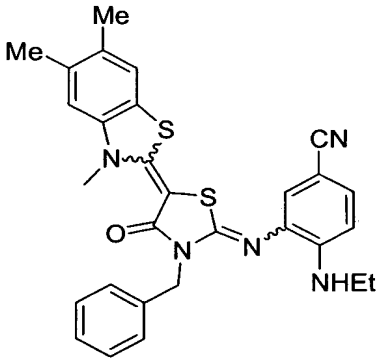
Preparation of 3-{3-benzyl-5-[3-methyl-6-trifluoromethoxy-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-6-(trifluoromethoxy)benzothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.18 (9H, m), 7.06 (1H, d), 6.49 (1H, d), 5.17 (2H, s), 3.81 (3H, s), 3.04-2.97 (2H, m), 1.03 (3H, t); MS(ESI): 582 (MH^+).

EXAMPLE 269

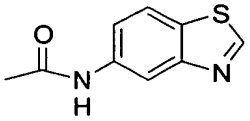
Preparation of 3-[3-benzyl-5-(3,5,6-trimethyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-5,6-dimethylbenzothiazole. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.20 (8H, m), 6.90 (1H, s), 6.48 (1H, d), 5.17 (2H, s), 3.80 (3H, s), 3.03-2.97 (2H, m), 2.35 (3H, s), 2.31 (3H, s), 1.02 (3H, t); MS(ESI): 526 (MH^+).

EXAMPLE 270

A. Preparation of 5-acetamidobenzothiazole



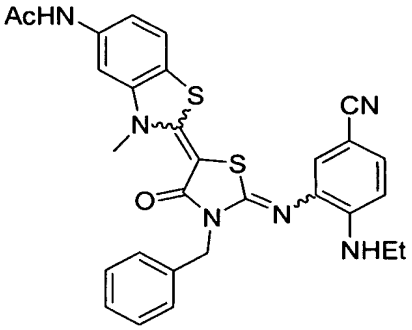
To a stirred solution of 4-chloro-3-nitroaniline (17.3 g, 100 mmol) in DCM (150 mL) was added dropwise acetic anhydride (14 mL, 150 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 2.5h. The solvent was removed in vacuo, and Et_2O was added to the residue. The precipitate was collected by filtration, washed with Et_2O, and dried in vacuo to give N-(4-chloro-3-nitrophenyl)acetamide (20.7 g, 96%), which was used without further purification.

A suspension of the above compound (13.8 g, 64.3 mmol) and $Na_2S{\cdot}9H_2O$ (18.6 g, 77.2 mmol) in DMF (100 mL) was stirred at ambient temperature under N_2 overnight. The reaction mixture was filtered, and the filtrate was diluted with water (400 mL) and then acidified with conc HCl to pH 3. The resulting yellow solids were collected by filtration, washed with water and dried under high vacuum to afford 4'-mercapto-3'-nitroacetanilide (12.0 g, 88%).

A suspension of 4'-mercapto-3'-nitroacetanilide (3.0 g, 14 mmol) and 10% Pd/C (0.6 g) in MeOH (200 mL) was hydrogenated at 60psi overnight. The catalyst was removed by filtration, and the filtrate was concentrated to give 3'-amino-4'-mercaptoacetanilide (2.5 g, 13 mmol), which was used in the next reaction immediately.

To a solution of intermediate 3'-amino-4'-mercaptoacetanilide in HOAc (50 mL) was added ethoxymethylene malononitrile (1.95 g, 16 mmol) and the resulting mixture was refluxed at 125°C for 5h. After cooling, the product mixture was concentrated under reduced pressure, and the residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The aqueous phase was extracted with EtOAc, and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 50:50) to give the title compound (508 mg, 17%) as a yellow solid. ^{1}H-NMR (DMSO-d_6): δ 9.35 (1H, s), 8.53 (1H, s), 8.10 (1H, d), 7.63 (1H, d), 2.15 (3H, s).

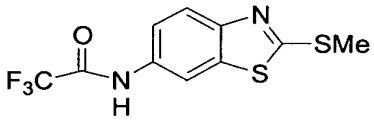
B. Preparation of 3-[3-benzyl-5-(3-methyl-5-acetamido-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylid neamino]-4-ethylaminobenzonitril



The title compound was prepared using the above 5-acetamidobenzothiazole as the starting material in a manner similar to that described in Example 265. ^{1}H-NMR ($CDCl_3$): δ 7.45-7.21 (8H, m), 6.62 (1H, dd), 6.48 (1H, d), 6.34 (1H, d), 5.17 (2H, s), 3.79 (3H, s), 3.02 (3H,s), 3.00 (2H, m), 1.02 (3H, t); MS(ESI): 555 (MH^+).

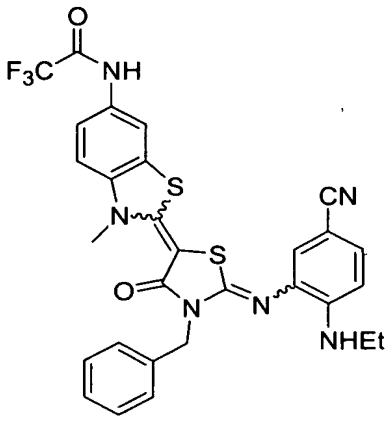
EXAMPLE 271

A. Preparation of 2-methylthio-6-(trifluoroacetoamido)benzothiazole



To a suspension of 6-amino-2-mercaptobenzothiazole (550 mg, 3.0 mmol) in anhydrous MeCN (15 mL) was added TEA (0.9 mL) and methyl *p*-toluenesulfonate (0.45 mL, 3.0 mmol) at ambient temperature. The mixture turned to a clear solution after a few minutes and was stirred at ambient temperature for 3h. To the above solution was added dropwise TFAA (0.65 mL, 4.6 mmol). After 12h the solution was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 10:90) to give the title compound (575 mg, 66%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.31 (1H, d), 7.99 (1H, br s), 7.84 (1H, d), 7.35 (1H, dd), 2.80 (3H, s).

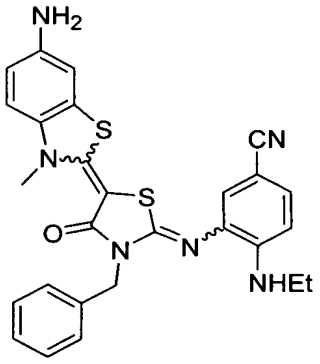
B. Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-6-ylid ne]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide



The title compound was prepared in a manner similar to that described in Example 265 by starting with 2-methylthio-6-(trifluoroacetamido)benzo-thiazole. ^{1}H-NMR (DMSO-d_6): δ 7.82 (1H, d), 7.40-7.06 (8H, m), 6.90 (1H, d), 6.48 (1H, d), 6.40 (1H, d), 4.89 (2H, s), 3.57 (3H, s), 2.83 (2H, m), 0.77 (3H, t); MS(ESI): 609 (MH^+).

EXAMPLE 272

Preparation of 3-[5-(6-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile

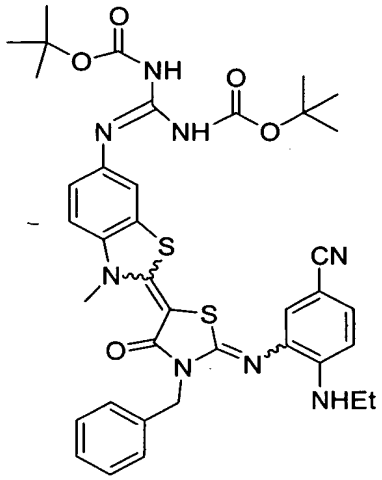


To the product of Example 271 (400 mg, 0.66 mmol) in a mixture of MeOH/H_2O (12 mL, 5:1 v/v) was added potassium carbonate (553 mg, 4.0 mmol). The reaction mixture was stirred at 60°C for 16h, and then concentrated under reduced pressure. The resulting residue was partitioned between $CHCl_3$ and water. The aqueous phase was extracted with $CHCl_3$, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give the title compound (326 mg, 97%) as a yellow solid. ^{1}H-

NMR (DMSO-d_6): δ 7.40-7.28 (6H, m), 7.15-7.13 (2H, m), 6.88 (1H, d), 6.66-6.61 (2H, m), 5.23 (2H, br s), 5.11 (2H, s), 3.75 (3H, s), 3.09-3.02 (2H, m), 1.01 (3H, t); MS(ESI): 513 (MH^+).

EXAMPLE 273

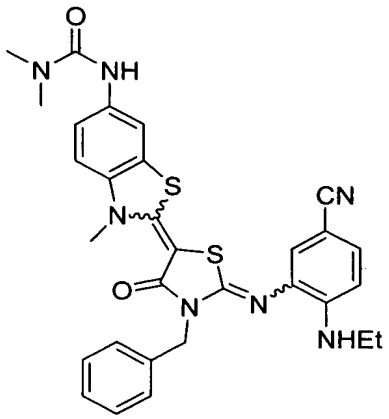
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N',N''-di(tert-butoxycarbonyl)guanidine



To a stirred mixture of the product of Example 272 (77 mg, 0.15 mmol), N, N'-di-(*tert*-butoxycarbonyl)thiourea (50 mg, 0.18 mmol) and TEA (70 μL, 0.5 mmol) in anhydrous DMF (1.5 mL) at 0°C was added $HgCl_2$ (49 mg, 0.18 mmol). The resulting mixture was stirred at 0°C for 30min, then at ambient temperature overnight. The mixture was diluted with $CHCl_3$, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (98 mg, 87%). ^{1}H-NMR ($CDCl_3$): δ 11.62 (1H, br s), 10.43 (1H, br s), 8.02 (2H, m), 7.45-7.20 (7H, m), 7.02 (1H, d), 6.49 (1H, t), 5.16 (2H, s), 3.82 (3H, s), 3.04-2.96 (2H, m), 1.43 (9H, s), 1.35 (9H, s), 1.02 (3H, t); MS(ESI): 756 (MH^+).

EXAMPLE 274

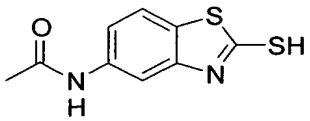
Preparation of 2-{2-[3-b nzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-1,1,-dimethylurea



To the product of Example 272 (89 mg, 0.174 mmol) in anhydrous $CHCl_3$ (5 mL) were added TEA (0.3 mL, 2.4 mmol) and dimethylcarbamyl chloride (0.2 mL, 2.0 mmol). The resulting mixture was stirred at ambient temperature overnight. After diluting with $CHCl_3$, the mixture was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 5:95) to afford the title compound (48 mg, 47%). ^{1}H-NMR ($CDCl_3$): δ 7.70 (1H, d), 7.44-7.26 (8H, m), 7.20 (1H, d), 7.00 (1H, d), 6.48 (1H, d), 6.38 (1H, s), 5.16 (2H, s), 3.79 (3H, s), 3.06 (6H, s), 3.05-2.97 (2H, m), 1.02 (3H, t); MS(ESI): 584(MH^+).

EXAMPLE 275

A. Preparation of 5-acetamido-2-mercaptobenzothiazole

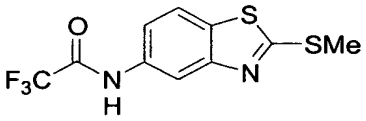


To a stirred solution of 4-chloro-3-nitroaniline (51.8 g, 0.36 mol) in anhydrous DCM (300 mL) was added dropwise acetic anhydride (45 mL, 0.48mol) at room temperature, and the resulting solution was stirred at room temperature for 3h. The solvent was removed in vacuo, and Et_2O was added to the residue. The precipitates were collected by filtration, washed

thoroughly with Et_2O, and dried under high vacuum to give 4'-chloro-3'-nitroacetanilide (78.7 g, 100%).

A mixture of $Na_2S \cdot 9H_2O$ (65 g, 0.28 mol), sulfur (25 g, 0.78 mol) and water (150 mL) were heated with stirring at 90°C for 10min, and then poured into a flask charged with the above 4'-chloro-3'-nitroacetanilide (21.5 g, 0.10 mol). The resulting mixture was heated at 80°C for 10min, and then CS_2 (12 mL, 0.2 mol) was added dropwise while maintaining a gentle reflux. The resulting mixture was heated at 90°C for 7h. The solids were collected by filtration, washed with water and dilute HCl solution. The solids were taken up in water, and the solution was made alkaline with solid NaOH. The solution was filtered, and the filtrate was acidified with conc HCl. The precipitates were collected by filtration, washed with water, and dried under high vacuum. The crude product was suspended in cold water (200 mL) and solid Na_2CO_3 was added to obtain pH 13. Dimethyl sulfate was added to the above milky solution, and the resulting mixture was stirred at ambient temperature for 3h. The solids were collected by filtration, washed with water, and dried under high vacuum to yield the title compound (12.4 g, 55%).

B. Preparation of 2-methylthio-5-(2,2,2-trifluoroacetamido)benzothiazole

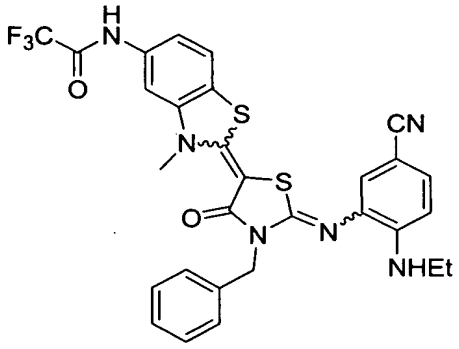


A suspension of 5-acetamido-2-mercaptobenzothiazole (12.9 g, 54 mmol) in a mixture of conc HCl (30 mL) and water (60 mL) was heated at reflux for 3h. After cooling, the mixture was extracted with $CHCl_3$, and the aqueous phase was diluted with ice-water. To the aqueous layer was added portionwise solid NaOH to achieve pH 6, and then solid K_2CO_3 to obtain pH 8. The precipitates were collected by filtration, washed with water, and dried under high vacuum to yield 5-amino-2-methylthiobenzothiazole (7.65 g, 72%).

To a stirred solution of 5-amino-2-methylthiobenzothiazole (3.93 g, 20 mmol) in anhydrous MeCN were added dropwise at 0°C TFAA (4.0 mL, 28 mmol) and TEA (5 mL, 36 mmol) under N_2. The mixture was stirred at room temperature for 3h. The solvent was removed in vacuo, and the residue was taken up in EtOAc, washed with water and brine, dried with Na_2SO_4, and

concentrated in vacuo. The crude material was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 20:80) to afford the title compound (3.9 g, 67%) as a pale white solid. ^{1}H-NMR ($CDCl_3$): δ 8.10 (1H, d), 7.98 (1H, br s), 7.75 (1H, d), 7.53-7.51 (1H, dd), 2.80 (3H, s).

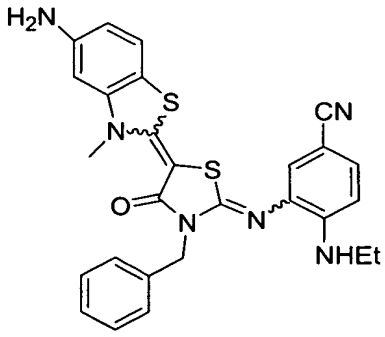
C. Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide



The title compound was prepared from 2-methylthio-5-trifluoroacetoamido-benzothiazole in a manner similar to that described in Example 265. ^{1}H-NMR (DMSO-d_6): δ 7.82 (1H, d), 7.56-7.26 (8H, m), 7.16 (1H, d), 6.51 (1H, d), 5.16 (2H, s), 3.83 (3H, s), 3.03-2.96 (2H, m), 1.02 (3H, t); MS(ESI): 609 (MH^+).

EXAMPLE 276

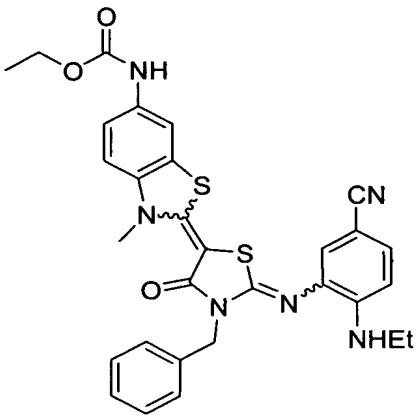
Preparation of 3-[5-(5-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 275 in a manner similar to that described in Example 272. ^{1}H-NMR (DMSO-d_6): δ 8.38 (1H, s), 7.47-7.36 (6H, m), 7.21 (1H, d), 6.69 (1H, d), 6.61-6.56 (2H, m), 4.45 (2H, br s), 5.18 (2H, s), 3.78 (3H, s), 3.12 (2H, m), 1.06 (3H, t) MS(ESI): 513 (MH^+).

EXAMPLE 277

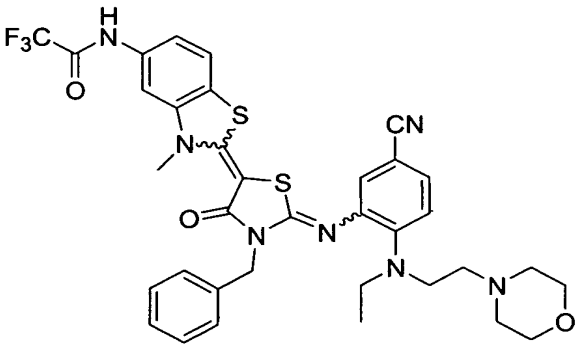
Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}carbamic acid ethyl ester



The title compound was prepared in a manner similar to that described in Example 274 by replacing dimethylcarbamyl chloride with ethyl choroformate. ^{1}H-NMR (DMSO-d_6): δ 9.64 (1H, s), 7.75 (1H, d), 7.29-7.16 (8H, m), 7.02 (1H, d), 6.51 (1H, d), 5.00 (2H, s), 4.04-3.98 (2H, q), 3.68 (3H, s), 2.97-2.91 (2H, m), 1.26 (3H, t), 0.88 (3H, t); MS(ESI): 585 (MH^+).

EXAMPLE 278

Preparation of N-[2-(3-benzyl-2-{5-cyano-2-[ethyl-(2-morpholin-ylethyl)amino]phenylimino}-4-oxothiazilidin-5-ylidene)-3-methyl-2,3-dihydrobenzothiazol-6-yl]-2,2,2-trifluoroacetamide

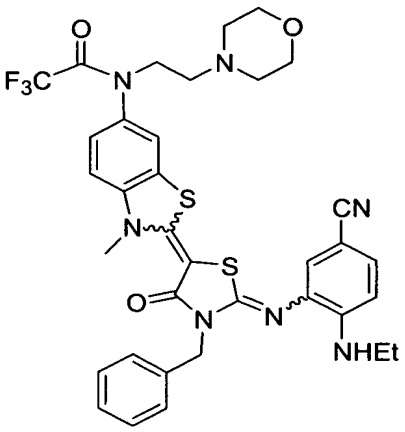


Sodium hydride (8 mg, 60% w/w in mineral oil, 0.2 mmol) was added at 0°C to a stirred solution of the product of Example 271 (52 mg, 0.1 mmol) in anhydrous DMF under N_2. The mixture was stirred at 0°C for 5min, then at ambient temperature for 15min. 4-(2-Chloroethyl)morpholine hydrochloride (24 mg, 0.15 mmol) was added to the above red solution at 0°C, and the

mixture was stirred at ambient temperature under N_2 for 21h. The reaction mixture was diluted with $CHCl_3$, washed thoroughly with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (42mg, 58%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.98 (1H, br s), 7.92 (1H, s), 7.68 (1H, s), 7.51-7.22 (7H,m), 6.81 (1H, d), 5.12 (2H, s), 4.04 (2H, m), 3.64 (5H, m), 3.36 (2H, m), 2.54-2.17 (8H, m), 1.26 (3H, m); MS(ESI): 722 (MH^+).

EXAMPLE 279

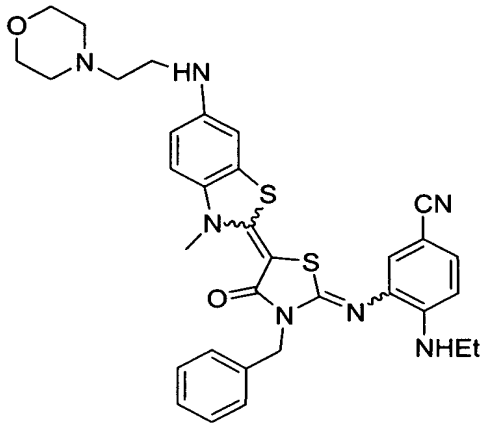
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide



To the product of Example 271 (65 mg, 0.11 mmol) in anhydrous DMF were added 4-(2-chloroethyl)morpholine hydrochloride (50 mg, 0.3 mmol), K_2CO_3 (30 mg, 0.21 mmol) and KI (10 mg). The reaction mixture was heated at 90°C for 30h, cooled, and diluted with $CHCl_3$. The solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (72 mg, 94%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.51 (1H, s), 7.44-7.42 (2H,m), 7.38-7.28 (5H, m), 7.19 (1H, d), 7.09 (1H, d), 5.18 (2H, s), 4.21 (2H, br s), 3.85 (3H, s), 3.68 (4H, br s), 3.05-2.96 (2H, m), 2.52-2.45 (6H, m), 1.03 (3H, t); MS(ESI): 722 (MH^+).

EXAMPLE 280

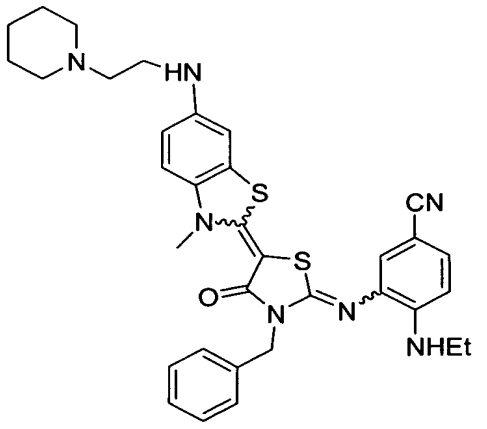
Preparation of 3-{3-benzyl-5-[3-m thyl-6-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 279 in a manner similar to that described in Example 272. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.21 (7H, m), 6.93 (1H, d), 6.78 (1H, d), 6.65 (1H, m), 6.48 (1H, d), 5.17 (2H, s), 3.81 (3H, s), 3.80-3.74 (4H, m), 3.20-3.17 (2H, m), 3.03-2.96 (2H, m), 2.67 (2H, br s), 2.49 (4H, br s), 1.02 (3H, t); MS(ESI): 626 (MH^+).

EXAMPLE 281

Preparation of 3-{3-benzyl-5-[3-methyl-6-(2-piperidin-1-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile

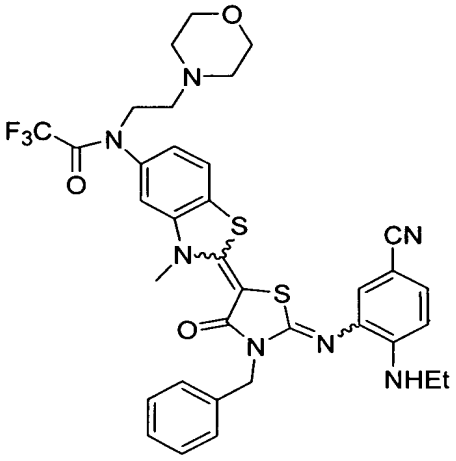


The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 4-(2-chloroethyl)piperidine hydrochloride. ^{1}H-NMR ($CDCl_3$):

δ 7.44-7.19 (7H, m), 6.93 (1H, d), 6.77-6.71 (2H, m), 6.48 (1H, d), 5.16 (2H, s), 3.77 (3H, s), 3.28 (2H, br s), 3.03-2.96 (2H, m), 2.81 (2H, br s), 2.48 (2H, br s), 2.04 (4H, br s), 1.02 (3H, t); MS(ESI): 624 (MH^+).

EXAMPLE 282

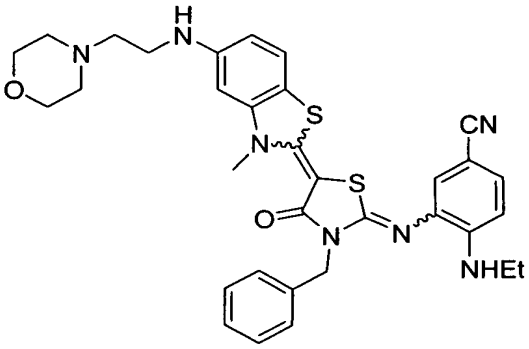
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide



The title compound was prepared from the product of Example 275 in a manner similar to that described in Example 279. ^{1}H-NMR ($CDCl_3$): δ 7.54 (1H, d), 7.44-7.11 (9H, m), 6.50 (1H, d), 5.18 (2H, s), 3.95 (2H, m), 3.79 (3H, s), 3.70 (4H, m), 3.04-2.98 (2H, m), 2.49 (6H, m), 1.03 (3H, t); MS(ESI): 722 (MH^+).

EXAMPLE 283

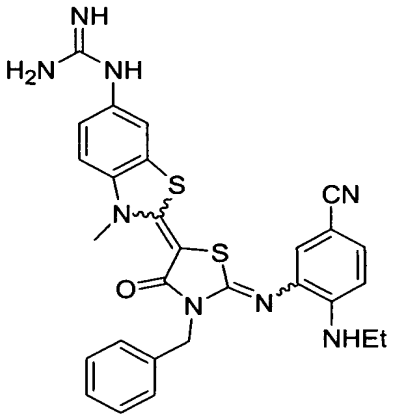
Preparation of 3-{3-benzyl-5-[3-methyl-5-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared from the product of Example 282 in a manner similar to that described in Example 272. ^{1}H-NMR ($CDCl_3$): δ 7.54 (1H, d), 7.44-7.11 (9H, m), 6.50 (1H, d), 5.18 (2H, s), 3.80 (2H, s), 3.70 (4H, br s), 3.04-2.98 (2H, m), 2.49 (6H, br s), 1.03 (3H, t); MS(ESI): 626 (MH^+).

EXAMPLE 284

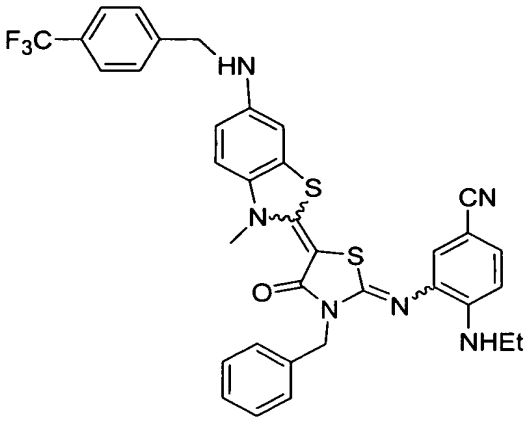
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}guanidine



To a stirred solution of the product of Example 273 (116 mg, 0.15 mmol) in anhydrous DCM (6 mL) was added TFA (3 mL) at 0°C. The reaction mixture was stirred at 0°C for 30min, then at ambient temperature for 14h. The solvent was removed in vacuo, and the residue was purified by reverse-phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H_2O (1:9 to 9:1) to afford the title compound (25 mg, 30%) as a yellow solid. ^{1}H-NMR (DMSO-d_6): δ 9.65 (1H, s), 7.72 (1H, d), 7.48 (1H, d), 7.41-7.25 (8H, m), 7.15 (1H, d), 6.65 (1H, d), 5.14 (2H, s), 3.84 (3H, s), 3.07 (2H, m), 1.01 (3H, t); MS(ESI): 555 (MH^+).

EXAMPLE 285

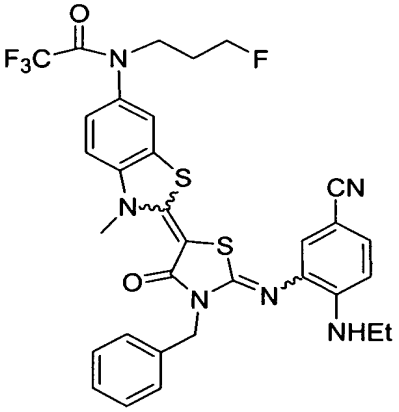
Preparation of 3-{3-benzyl-5-[3-methyl-6-(4-trifluoromethylbenzylamino)-3*H*-benzothiazol-2-yliden]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 4-(trifluoromethyl)benzyl bromide. ^{1}H-NMR (DMSO-d_6): δ 7.69 (2H, d), 7.58 (2H, d), 7.38-7.32 (6H, m), 7.17 (1H, d), 7.14 (1H, d), 6.94 (1H, d), 6.63 (1H, dd), 6.61 (1H, d), 5.10 (2H, s), 4.40 (2H, s), 3.73 (3H, s), 3.05 (2H, m), 1.00 (3H, t); MS(ESI): 671 (MH^+).

EXAMPLE 286

Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-fluoropropyl)-2,2,2-trifluoroacetamide

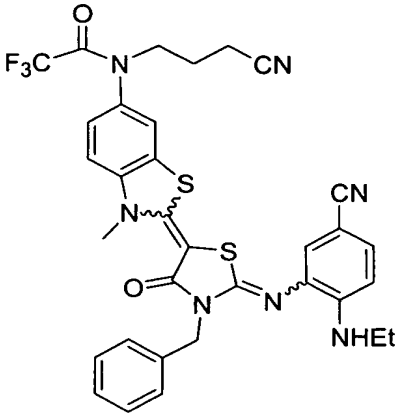


The title compound was prepared in a manner similar to that described in Example 279 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 1-bromo-3-fluoropropane. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.19 (9H, m), 7.10 (1H, d),

6.50 (1H, d), 5.18 (2H, s), 4.60 (1H, m), 4.48 (1H, m), 4.20 (1H, m), 3.91 (1H, m), 3.83 (3H, s), 3.01 (2H, m), 2.09-1.99 (2H, m), 1.03 (3H, t); MS(ESI): 669 (MH^+).

EXAMPLE 287

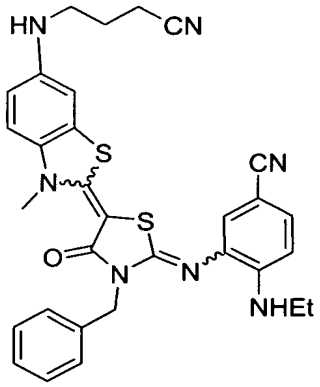
Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-cyanopropyl)-2,2,2-trifluoroacetamide



The title compound was prepared in a manner similar to that described in Example 279 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 4-bromobutyronitrile. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.19 (9H, m), 7.11 91H, d), 6.51 91H, d), 5.19 (2H, s), 3.86 (3H, s), 3.85-3.77 (2H, m), 3.05-2.98 (2H, m), 2.53-2.44 (2H, m), 2.04-1.88 (2H, m), 1.03 (3H, t); MS(ESI): 676 (MH^+).

EXAMPLE 288

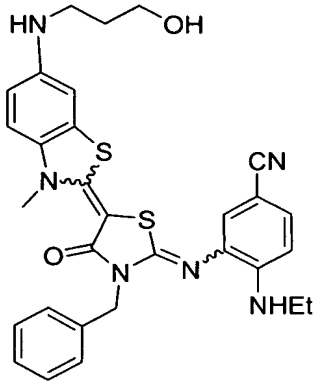
Preparation of 3-{3-benzyl-5-[6-(3-cyanopropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



The title compound was prepared from the product of Example 287 in a manner similar to that described in Example 272. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.20 (7H, m), 6.94 (1H, d), 6.77 (1H, d), 6.65 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.77 (3H, s), 3.34 (2H, m), 3.01 (2H, m), 2.49 (2H, m), 2.01 (2H, m), 1.02 (3H, t); MS(ESI): 580 (MH^+).

EXAMPLE 289

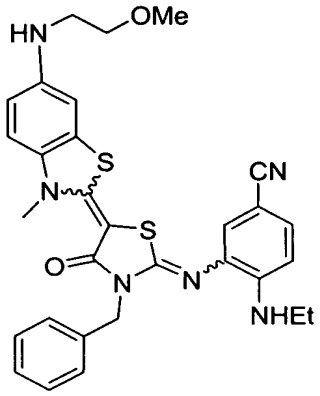
Preparation of 3-{3-benzyl-5-[6-(3-hydroxypropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 3-bromopropanol. ^{1}H-NMR ($CDCl_3$): δ 7.44- 7.21 (8H, m), 6.93 (1H, d), 6.79 (1H, d), 6.65 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.85 (2H, m), 3.77 (3H, s), 3.30 (2H, t), 3.01 (2H, m), 1.92 (2H, m), 1.02 (3H, t); MS(ESI): 571 (MH^+).

EXAMPLE 290

Preparation of 3-{3-benzyl-5-[6-(2-methoxyethylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamin)benzonitrile



The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 2- bromoethyl methyl ether. ^{1}H-NMR ($CDCl_3$): δ 7.44-7.21 (7H, m), 6.93 (1H, d), 6.79 (1H, d), 6.66 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.77 (3H, s), 3.63 (2H, m), 3.41 (3H, s), 3.30 (2H, m), 3.00 (2H, m), 1.02 (3H, t); MS(ESI): 571 (MH^+).

EXAMPLE 291

In Vivo studies

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted from frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by FXR, knock out mice ($FXR^{-/-}$) and C57BL/6 wild-type controls may be used in this same protocol.

Plasma Lipid Evaluation

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day –1 (in order to group animals), day 1, 3, and 7. Samples are collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted from frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by FXR knockout mice and C57BL/6 wild-type controls [maybe] may be used in this same protocol.

Cholesterol Absorption

Evaluation of compounds to inhibit cholesterol absorption is done via measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of the study, animals are administered [^{14}C]-cholesterol and [^{3}H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to evaluate the amount of cholesterol absorbed by the individual animal.

Since modifications will be apparent to those of skill in this art, it is intended that the subject matter claimed herein be limited only by the scope of the appended claims.